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Contents

No. 1, July 1965

Medical Implications of High Oxygen Pressures (*Alvarenga Lecture XXIV*) ..... Christian J. Lambertsen 1

Immunologic Mechanisms in Glomerulonephritis: Hypersensitivity and Autoimmunity (*Thomas Dent Mütter Lecture LXXVII*) Robert C. Mellors 19

Preventive Medicine in Medical Education: An Internist's Viewpoint (*James M. Anders Lecture XXXXIV*) ..... John R. Ellis 28

The Woman's Medical College of Pennsylvania Catharine Macfarlane 39

Ann Preston: Dean of The Woman's Medical College of Pennsylvania, 1866–1872 ..... Marion S. Fay 43

Dr. Chevalier Jackson: President of The Woman's Medical College of Pennsylvania, 1935–1941 ..... Emily Lois Van Loon 49

Memoir of Bernard Mann (1883–1964) ..... Lewis C. Scheffey 52

No. 2, October 1965

A Treatment of Burns (*Nathan Lewis Hatfield Lecture IL*) Carl A. Moyer 53

The History and Significance of Serendipity in Medical Discovery (*Edward Bell Krumbhaar Prize Essay VI*) ..... Ronald E. Rossman 104

Benjamin Rush's Medical Thesis, "On the Digestion of Food in the Stomach", Edinburgh, 1768. (Translation and Historical Introduction) ..... David F. Musto 121

Dr. Jules L. Prevost and the Teaching of Medical History at Temple University School of Medicine, 1910–1965 ..... Fred B. Rogers 139

Transactions of the Sections: Programs and Abstracts of the Section on General Medicine 147

No. 3, January 1966

The Human Heart: Some Aspects of its Excitation (*Mary Scott Newbold Newbold LXXXIX*) ..... Dirk Durrer 159

Drug Antigens and the Diseases Which They Produce (*Hira S. Chouké Lecture VI*) ..... Max Samter 171

The Central Lymphoid Tissue in Developmental Immunobiology (*Mary Scott Newbold Lecture LXXXVII*) ..... Robert A. Good et al. 180

Community Mental Health Care in Britain? ..... Henry R. Rollin 186

Behavioral Reaction to Surgical Procedures ..... Floyd S. Cornelison 194

John Hunter (1728–1793): Creative Surgeon ..... Bernard L. Segal 197

Dr. Paul-Ferdinand Gachet: Vincent Van Gogh's Last Physician Remo Fabbri, Jr. 202

Memoirs:

Albert Schweitzer (1875–1965) ..... Fred B. Rogers 209

Roy W. Mohler (1892–1964) ..... John B. Montgomery 213

Charles E. G. Shannon (1875–1965) ..... Sidney G. Radbill 215

Norman M. MacNeill (1886–1965) ..... Edward L. Bauer 216

232502

No. 4, April 1966

President's Address (*President's Annual Report*) . . John H. Gibbon, Jr. 219
The Primate Socialization Motives (*Alvarenga Lecture XXV*)
Harry F. Harlow 224
Virus-Induced Synthesis of Enzymes (*Nathan Lewis Hatfield Lecture L*)
Seymour S. Cohen 238
The University in the Forefront of Community Action
William A. Steiger 249
David Hayes Agnew, M.D. (1818–1892) . . . . . Samuel X Radbill 252
Felice Fontana (1720–1805): The Forgotten Physiologist
Joseph R. Di Palma 261
Library Historical Notes . . . . . W. B. McDaniel, 2d 264
A Decade of Harvest: *Ave atque vale* to the Editor, Fred B. Rogers, M. D.
W. B. McDaniel, 2d 267

Memoirs

Lovett Dewees (1880–1965) . . . . . Emily Hartshorne Mudd 269
Alexander Garrison Fewell (1884–1965) . . . . . Warren S. Reese 271
William Parks Belk (1889–1965) . . . . . Edward Rose 273
John Thompson Farrell, Jr. (1897–1965) . . . . . Mario A. Cinquino 275
Albert Americo Martucci (1900–1965) . . . . . Elmer J. Elias 277

Annual Reports

Secretary, 279; Treasurer, 281; Library, 285; Mütter Museum and College Collections, 300.
List of College Lectures, 1965 303
Transactions of the Sections 304
Officers, Committees, Sections and Administrative Staff of the College 1966 305
List of Fellows 309
Suggested Form of Bequest 335
Index to Volume 33 336

TRANSACTIONS & STUDIES
of the
College of Physicians of Philadelphia

Volume 33
(Fourth Series)

Number 1
(July 1965)

Medical Implications of High Oxygen Pressures[1]

By CHRISTIAN J. LAMBERTSEN, M.D.[2]

THE rational use of high oxygen pressures in medicine is related to a simple but fundamental physical study performed by a Fellow in another distinguished College. William Henry reported his findings in the Philosophical Transactions of the Royal Society of London, 1803, relating gas pressure and the solubility of gases in water, as follows: "But, as the spaces occupied by every gas are inversely as the compressing force, it follows, *that water takes up, of gas condensed by one, two, or more additional atmospheres, a quantity which ordinarily compressed, would be equal to twice, thrice, &c. the volume absorbed under the common pressure of the atmosphere.*" This statement, now well known as Henry's Law, means that by administration of oxygen in a compression chamber it is possible to drive large amounts of oxygen into physical solution in the arterial blood. One result of improved arterial oxygen content, even without improvement in cardiac function, is an increase in what can be considered "cardiac oxygen output" and "tissue oxygen flow".

An equally important consequence of exposure of the blood to high oxygen pressure in the lungs is the increased oxygen partial pressure in the arterial blood flowing into the tissues, which provides a greater pressure head for diffusion of oxygen from the capillary to the metabolizing cell. These two related forms of improved arterial oxygenation are important in conventional inhalational therapy at one atmosphere. Examples of conditions in which an increase of inspired oxygen pressure to several atmospheres may provide still further therapeutic gains are shown in Figure 1. In most of the examples cited the practical utility of high oxygen pressures has been inadequately appraised.

In many clinical states, death of the cell or death of the individual is due to an inadequacy of oxygenation. Figure 1 emphasizes conditions in which gains may be proportional to the degree of hyperoxygenation. Purposely omitted from the figure are situations such as narcotic or other respiratory depressions, where the lungs and circulation are competent and hypoxia is readily overcome by oxygen administration at one atmosphere in a hospital room.

Treatment of disease by exposing patients to an environment of compressed air, but not to pure oxygen, was carried out by physicians in several countries during the 19th century (32). These included men of stature such as

[1] Alvarenga Lecture XXIV. The College of Physicians of Philadelphia, 2 December 1964.

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MEDICAL IMPLICATIONS OF HIGH OXYGEN PRESSURES

DEFECTIVE PULMONARY O_2 UPTAKE	PULMONARY EDEMA HYALINE DISEASE ATELECTASIS
DEFECT IN O_2 TRANSPORT BY BLOOD	CARBON MONOXIDE POISONING METHEMOGLOBINEMIA SEVERE HEMORRHAGE
DEFECT IN TISSUE BLOOD FLOW	CORONARY OCCLUSION
	THROMBOSIS, THROMBOEMBOLISM ← MESENTERIC, PERIPHERAL ART, PULMONARY
	AEROEMBOLISM AND BENDS
RADIATION THERAPY OF NEOPLASMS	
ANAEROBIC INFECTIONS	GAS GANGRENE TETANUS
SURGICAL PROCEDURES	PLASTIC SURGERY CARDIOVASCULAR SURGERY NEUROSURGERY

FIG. 1.

Forlanini of Italy, who is better known for his contributions to the technique of artificial pneumothorax (24) (Fig. 2). The early employment of air compression chambers, including a pressurized, mobile operating room constructed in 1879 (23), had no clear therapeutic basis. Even as late as 1930, a massive, five-story, 60 room, 64 foot diameter, spherical compressed air chamber in Cleveland, Ohio was used in the scientifically irrational treatment of such disorders as diabetes, syphilis and neoplasms (20) (Fig. 3). The Bureau of Investigation of the American Medical Association was unsuccessful for several years in condemning this "therapy" (11), but eventually it was discontinued. The giant chamber was demolished in 1942 and undoubtedly contributed heavily to the success of rearmament for World War II.

It is evident, then, that pressure therapy is not new. However, except for some very limited explorations by Priestley with Phlogiston, his newly discovered oxygen (41), and the extensive investigational efforts of Paul Bert in the late 1800's (5), medical interest in compressed gases was not truly based on rational concepts of increased oxygenation.

Reason appeared only after therapy by administration of oxygen itself was begun, and reason did not appear all at once. Largely due to the interest and work of Barach (1), the therapeutic use of oxygen at normal atmospheric pressures became widespread prior to World War II. Between 1940 and the present time, physiological studies related to aviation and diving medicine have led to further understanding of the physiological and toxic effects of oxygen. They have also awakened interest in the possible applications of very high oxygen pressures to clinical problems.

Probably the first important medical use of pure oxygen administration at several atmospheres pressure was to speed the elimination of helium after a deep, helium-oxygen dive, and thus minimize the likelihood of decompression sickness (3). Much later, oxygen was administered to schizophrenic patients at four atmospheres absolute pressure in a clinical study of "oxygen convulsions" as a substitute for the standard electroshock procedure (Unpublished observations, Ewing, J. H., Lambertsen, C. J., Freyhan, F. A., Kough, R., Stroud, M. W., and Gould, R.). Next, oxygen at high pressures began to be used as a means of increasing the sensitivity of tumors to therapeutic ionizing radiation (15). Then, in about 1956, the concept of "oxygen drenching" was proposed as a means of prolonging the viability of organs subsequently subjected to circulatory arrest (6). Therapy of the reversible poisoning

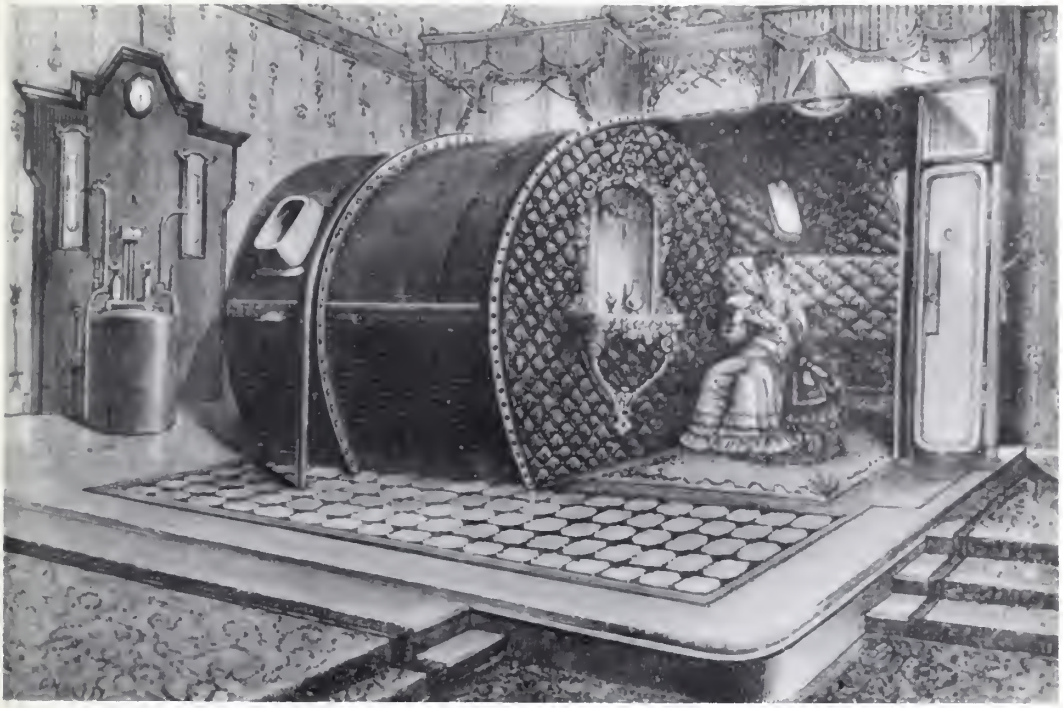

FIG. 2. Luxurious compression chamber used by Forlanini in 1875 (24).

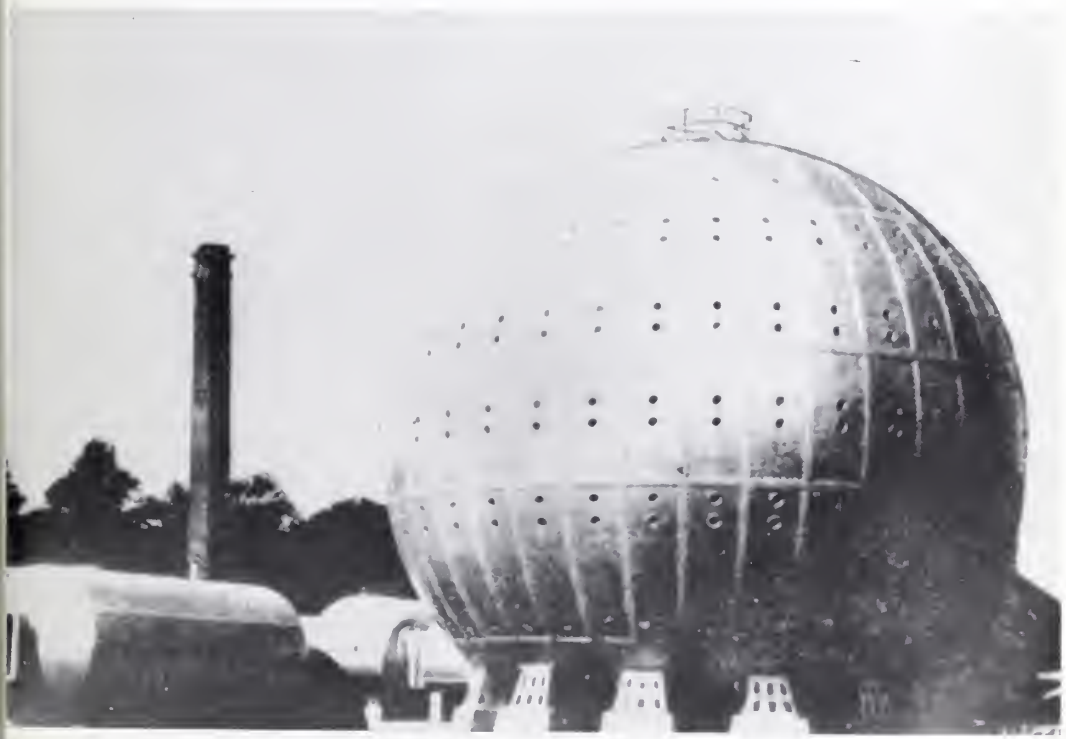

FIG. 3. Giant, multi-roomed pressure sphere built in Cleveland, Ohio and used by Cunningham.

due to specific chemical binding of carbon monoxide to hemoglobin, studied early (28), began to receive renewed attention (22, 40, 44). Eventually, high oxygen pressures were successfully applied to the treatment of Clostridial infections such as gas gangrene (9, 10), and to the relief of bends (47). As is usual when interest outstrips the capacity for obtaining information, the extensive clinical application of high oxygen pressures to medical and surgical problems has temporarily outstripped its evaluation through controlled basic and clinical studies (36). For this reason it is especially important to consider the fundamental effects of hyperoxygenation.

Physiological Basis for Oxygenation At Increased Ambient Pressure

"Oxygen Drenching" and the Duration of Tissue Oxygen Stores

As warm-blooded animals, we are dependent upon a continuing supply of oxygen to the metabolizing tissues. Tissue stores of oxygen in physical solution are normally extremely small and, as shown in Table I, arrest of the circulation should lead to use within about 3 seconds of the minute amount of oxygen stores of brain tissue (25). The result is unconsciousness followed by progressive tissue destruction. The table shows further that administration of pure oxygen at 1.0, 2.0, 3.0 atmospheres and higher pressures will lead to an increase of tissue oxygen stores. However, due to the high rate of normal brain metabolism, any extension of consciousness, cell function and survival following circulatory arrest will be measured in seconds, even at 3.0 atmospheres. Hypothermia will increase this time, but periodic reestablishment of blood flow is necessary for survival.

Factors In Tissue Oxygenation

Whole body oxygenation. The dynamics of normal cellular oxygenation depend not only upon the entering partial pressure of oxygen (Po_2 in mm Hg) and the amount of oxygen flow but also upon the diffusion distance from capillary to cell, the characteristic resistance of the tissue to diffusion, and the rate at which the metabolizing cell is consuming oxygen. The available information concerning the relationships of these factors has been described in several presentations (16, 25).

The overall normal daily oxygen uptake and metabolism (Table II) reflects the amazing capacity of the physiological mechanisms to obtain and deliver oxygen to the cells. In one day a normal individual, pumping nearly 8000 liters of blood, consumes about 368 liters of oxygen from the much larger amount which is circulated through his tissues. The digestive system requires the greatest amount of this, but the needs of the brain are almost as large.

Gas exchange across a tissue vascular bed. The relationships among entering (arterial) oxygen tension, blood flow, metabolism, and blood oxygen transport are shown diagrammatically in Figure 4. The figure is designed to show the average of the events in all the capillaries in an organ such as the brain. An arterial, a capillary and a venous section are shown; the capillary section represents both

TABLE 1

THE QUESTION OF OXYGEN "DRENCHING" AND ISCHEMIC TISSUE SURVIVAL

GAS BREATHED	CELL O_2 STORES (Estimated Mean)	DURATION OF CONSCIOUSNESS * ON VENTRICULAR ARREST	RATE OF CELL DEATH
AIR, 1 ATM.	0.2 cc/100 Gm	3 seconds	?
O_2, 1 ATM.	0.4 cc/100 Gm	6 seconds	?
O_2, 2 ATM.	1.1 cc/100 Gm	15 seconds	?
O_2, 3 ATM.	1.9 cc/100 Gm	29 seconds	?

*Estimated at normal brain O_2 consumption of 3.5 cc O_2/100 Gm brain tissue per minute, cell oxygen stores exclusive of capillary hemoglobin.

TABLE 2

	MASS KG.		
WHOLE BODY	63	3.4	7,200
	2.7	7	2,160
	2.7	1	1,836
	21	71	1,...
	1....	2.1	1,...
	3.6	1	684
	1.3	1.1	324
	24	1....	547

the length of the capillary and the time of blood passage through the capillary bed. The measured values shown are those for normal (resting, air-breathing) arterial and internal jugular venous blood. From these and values for blood oxygen capacity, the rate of fall in P_{O_2} along the capillary has been calculated on the assumption that the rate of oxygen loss to the tissue is uniform. The figure emphasizes that, even with a normal entering arterial P_{O_2}, severe and damaging cellular anoxia can result from any of several disorders which reduce the rate of oxygen flow through the capillary. However, in tissues poisoned by cyanide, oxygen metabolism will be suppressed and failure of intracellular oxidations will occur in the presence of *greater* than normal oxygenation. Finally, if blood flow and oxygen carrying capacity are sustained, a state of lowered arterial P_{O_2} may still provide sufficient oxygen to prevent damaging cellular anoxia.

The fall in P_{O_2} from red cell to mitochondrion. Figure 4 emphasizes several types of alterations in the capillary P_{O_2} which are important primarily because they influence delivery of oxygen to points of oxidative activity within the metabolizing cell. Figure 5, constructed from indirect measurements summarized elsewhere (25), illustrates reasonable values for diffusion distance from a capillary and for the fall in oxygen pressure from the indicated mean capillary oxygen tensions. Note that these estimates suggest a gradient of about 2 mm Hg from hemoglobin molecule to the capillary wall, and up to as much as 25 mm Hg to a distant cell. A gradient of only 1 mm Hg

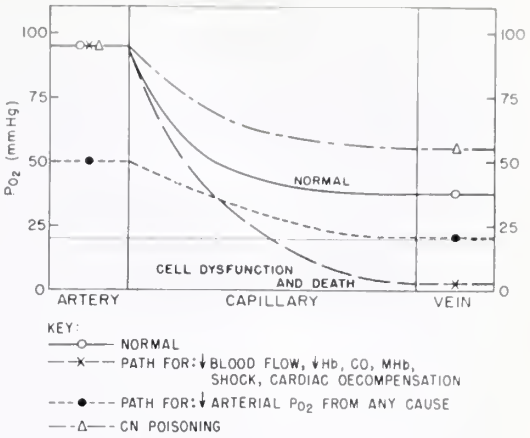

FIG. 4. Tissue capillary gas exchange.

suffices to transfer oxygen across the cell itself and about 0.1 mm Hg permits diffusion within the mitochondrion where the essential oxidative processes occur (25).

THE EFFECTS OF HIGH OXYGEN PRESSURES UPON OXYGENATION OF BLOOD AND TISSUES

During air breathing at sea level, arterial hemoglobin saturation is normally close to 100 percent (about 97–98% saturated) (37). For this reason, oxygen administration at any pressure to individuals with normal arterial oxygenation can produce only a slight, and therapeutically insignificant, increase in chemically bound oxygen. However, the increase in physically dissolved oxygen produced by oxygen administration (about 2.14 ml O_2/100 ml of blood per atmosphere) is extremely important. At an inspired oxygen pressure of three atmospheres, for example, over six ml of additional oxygen is driven into physical solution in the water of the blood. Figure 6 shows the addition of this physically dissolved oxygen as a slight, linear rise of the lower oxygen uptake curve. In the upper curve which depicts the characteristics of hemoglobin oxygen uptake and release in the normal state at sea level, A and V represent average values for arterial and mixed venous oxygenation. The fall in P_{O_2} across the tissue capillary bed during air breathing is seen to be close to 50 mm Hg. When oxygen is breathed at three

atmospheres, the removal of physically dissolved oxygen from the blood in the tissue capillaries leads to an extreme fall in oxygen tension, as great as several thousand mm Hg. Thus, at three atmospheres in an actively metabolizing organ like the brain, the tissue oxygen requirement is so great that the oxygen pressure of blood is lowered until, after most of the physically dissolved oxygen has been used, some of the oxygen held by hemoglobin is released.

If the partial pressure of oxygen in the arterial blood is sufficiently elevated, it should be possible to supply the oxygen needs of the tissues entirely by oxygen in physical solution. This condition has been approached in animals severely poisoned by carbon monoxide (28), in an animal whose blood was almost completely replaced by hemoglobin free solutions (7), and in men exposed to pure oxygen at 3.5 to 4.0 atmospheres pressure (34).

It is important to realize that in normal individuals, even three atmospheres of inspired oxygen will not provide extreme and equal elevation of P_{O_2} in all tissues. Table III and Figure 7 are based upon average normal values for organ blood flow and metabolism and upon the influence of inspired oxygen pressure upon arterial oxygen content; they provide estimates of the rises in venous oxygenation expected from oxygen administration to normal subjects at three atmospheres pressure (34). Clearly, the "dose" of oxygen should not be expected to be the same for each tissue. An organ such as the kidney, which has a blood flow disproportionately high even for its active metabolism, may be exposed to a greater mean tension of oxygen than the liver or the constantly exercising heart. In Table III the only actual measurements for high oxygen effect upon organ venous blood are those for the brain; the other values were calculated to emphasize the order of magnitude of oxygen effects to be expected. Certainly to completely supply oxygen to all cells by way of physical

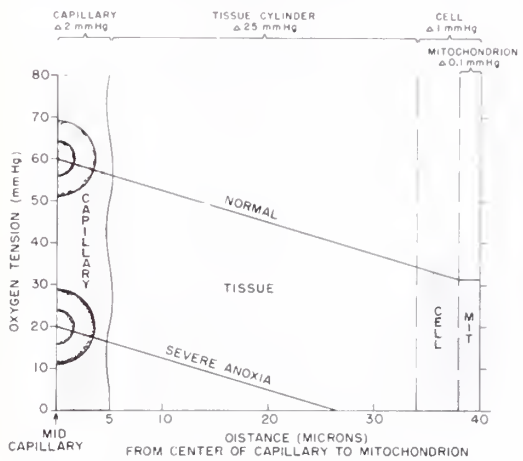

FIG. 5. The fall in P_{O_2} from red cell to cell mitochondrion.

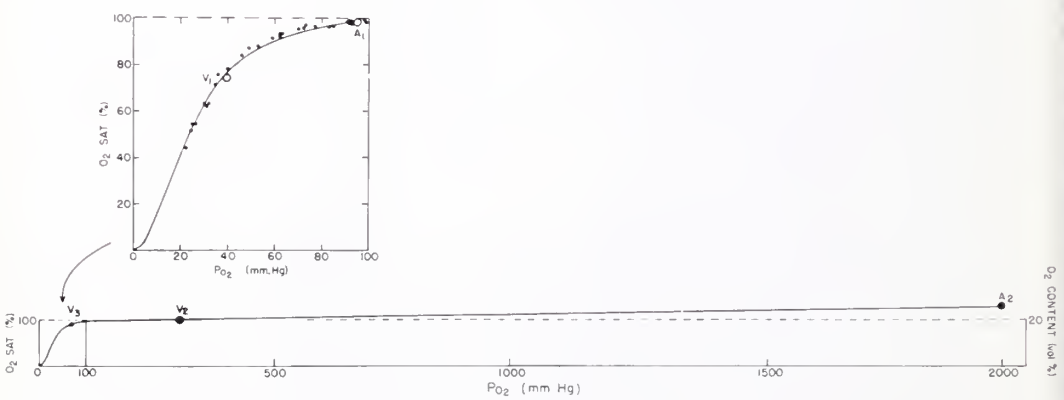

FIG. 6. Comparison of oxyhemoglobin dissociation curve during air breathing at sea level with oxygen uptake curve breathing oxygen at 3.5 atmospheres. The slope of the oxygen uptake curve above complete saturaton of hemoglobin represents the physical solution of oxygen in the water of blood (From Lambertsen, C. J., *Handbook of Physiology* (34)).

TABLE 3

EFFECT OF O_2 AT 3.0 ATM. ON OXYGENATION

ORGAN OR TISSUE	BLOOD FLOW ml/100G/min	O_2 USE ml/100G/min	$A-V O_2$ ml/100ml	AIR BREATHING VENOUS P_{O_2} mm Hg	OXYGEN BREATHING VENOUS P_{O_2} mm Hg
HEART	84	9.7	11.4	21	40
BRAIN	54	3.3	6.2	35	50
MUSCLE	3	0.16	6.0	36	300
HEPATIC-PORTAL	58	1.96	3.4	46	900
SKIN	13	.33	2.5	52	1190
KIDNEY	420	6.0	1.4	63	1543
CAROTID BODY	2000	9.0	.15	100	1900

solution it will be necessary to grossly raise inspired P_{O_2} above three atmospheres, to reduce tissue metabolism by anesthetics or hypothermia, or to increase the blood flow in the tissues (34).

The combination of hypothermia and hyperoxygenation deserves continued attention. The physical solubility of oxygen in body fluids increases as body temperature is lowered. This is relatively unimportant during air breathing at sea level. However, as inspired oxygen pressure is raised, e.g. to two or three atmospheres (Figure 8), marked improvement in oxygen transport is produced by tolerable hypothermia. When to these factors are added the suppression of metabolic demand for oxygen and the probable increase in tolerance to oxygen poisoning during hypothermia, it becomes likely that the combination of the two measures may provide for more than additive benefits (34).

The extreme effect and the importance of alternations in blood flow through an organ during hyperbaric oxygenation is evident in Figure 9, which summarizes the results of many experiments in normal men (34). The illustrated path of fall in mean oxygen pressure across the capillary bed is calculated (38) from measurements of arterial and internal jugular venous oxygen tension. Since oxygen administration leads to a moderate cerebral vasoconstriction in normal men, as mentioned

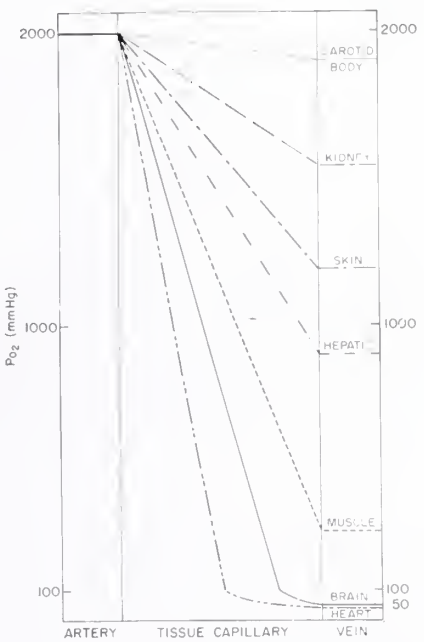

FIG. 7. The influence of high oxygen pressure on organ oxygenation.

above, even 3.5 atmospheres of inspired P_{O_2} does not prevent the use of some oxygen from hemoglobin. However, when brain vessels are dilated by administering carbon dioxide with the oxygen (upper curve), an approximately 1000 mm Hg rise in brain venous P_{O_2} occurs (38).

Carbon dioxide transport function is also modified by hyperoxygenation. The prevention

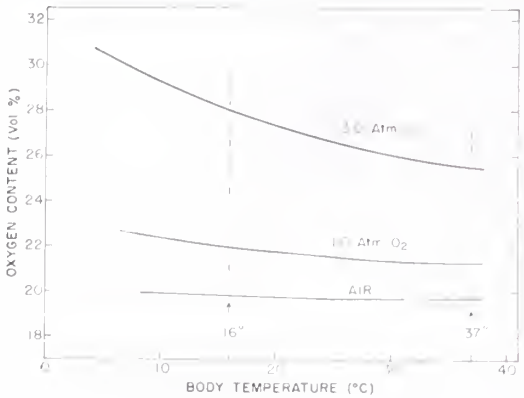

FIG. 8. The effect of hypothermia and oxygen administration on blood oxygenation.

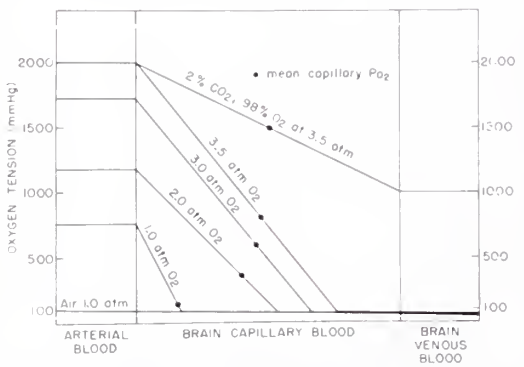

FIG. 9. Diagram of changes in blood P_{O_2} during passage of blood through brain capillary in man, based upon measurements of arterial and internal jugular venous blood.

of hemoglobin reduction interferes with the release of base which normally aids in the buffering of carbon dioxide. The result is a definite rise in tissue P_{CO_2}, which in the brain is self-limited to about five mm Hg (34). This rise in tissue acidity has considerable physiological interest but should not, as in the past, be thought to produce the toxic effects of oxygen breathing.

Acute Physiological Effects of Oxygen

This lecture, with its emphasis upon the therapeutic aspects of hyperbaric oxygenation, does not allow full consideration of the harmless and reversible actions of oxygen upon normal processes. Figure 10 summarizes only a few of the effects of oxygen observed in normal men and animals. These physiological effects include not only the alterations of oxygen and carbon dioxide transport already considered, but also a concurrently stimulant and depressant effect upon respiration, constriction of cerebral, retinal and renal vessels, suppression of the normal chemoreflex response to carbon dioxide administration, and diminution of sympathetic tone. The figure shows that following oxygen administration a number of adjustments are made which result in the establishment of a series of new equilibrium states (34). The actions of oxygen, of interest in their own right, have additional importance as potential modifiers of the responses to drugs used as adjuncts in pressure therapy.

Hyperbaric Oxygenation In Specific Medical Conditions

Although the use of oxygen at one atmosphere is not yet being fully exploited in medicine, several clinical situations are now receiving considerable attention as subjects for study of oxygen therapy at several atmospheres pressure. The most important of these are as follows:

Bends and air embolism. These are quite different conditions. In air embolism air enters the circulation from an external source such as an overdistended lung, or during cardiovascular surgery or a neurosurgical procedure. In bends the nitrogen dissolved in tissues during an exposure to increased pressure forms bubbles in the tissues when the pressure is lowered too rapidly to permit normal elimination of nitrogen via the circulation and lungs.

The problem in both bends and air embolism is to dissolve the circulation-obstructing and tissue-distorting bubbles so that the nitrogen can be harmlessly transported to the lungs as a gas in solution. The classical Navy treatment of bends, recompression with air to six atmospheres to reduce the bubble to about one-sixth its size, is effective. However, resolution of the compressed bubbles is very slow, since the compressed air breathed itself contains nitrogen

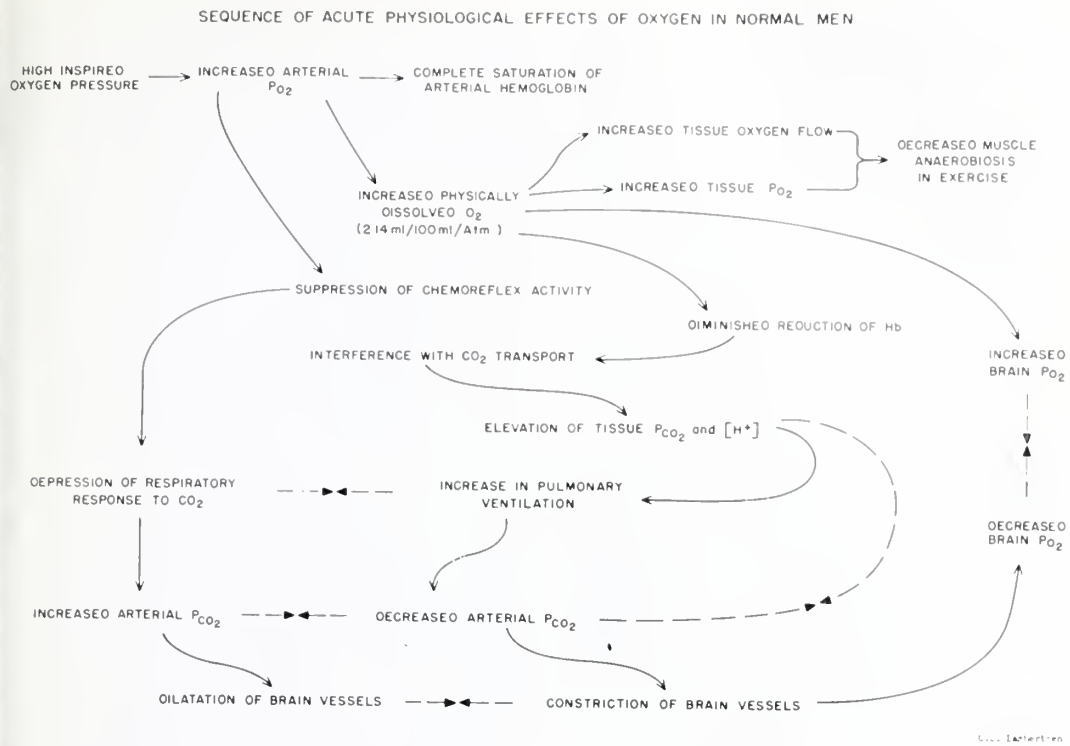
SEQUENCE OF ACUTE PHYSIOLOGICAL EFFECTS OF OXYGEN IN NORMAL MEN
HIGH INSPIREO OXYGEN PRESSURE
INCREASEO ARTERIAL P_{O_2}
COMPLETE SATURATION OF ARTERIAL HEMOGLOBIN
INCREASEO TISSUE OXYGEN FLOW
INCREASEO TISSUE P_{O_2}
OECREASEO MUSCLE ANAEROBIOSIS IN EXERCISE
INCREASEO PHYSICALLY DISSOLVEO O_2 (2.14 ml/100 ml/Atm)
SUPPRESSION OF CHEMOREFLEX ACTIVITY
OIMINISHEO REDUCTION OF Hb
INTERFERENCE WITH CO_2 TRANSPORT
INCREASEO BRAIN P_{O_2}
ELEVATION OF TISSUE P_{CO_2} and $[H^+]$
OEPRESSION OF RESPIRATORY RESPONSE TO CO_2
INCREASE IN PULMONARY VENTILATION
OECREASEO BRAIN P_{O_2}
INCREASEO ARTERIAL P_{CO_2}
OECREASEO ARTERIAL P_{CO_2}
OILATATION OF BRAIN VESSELS
CONSTRICTION OF BRAIN VESSELS

FIG. 10.

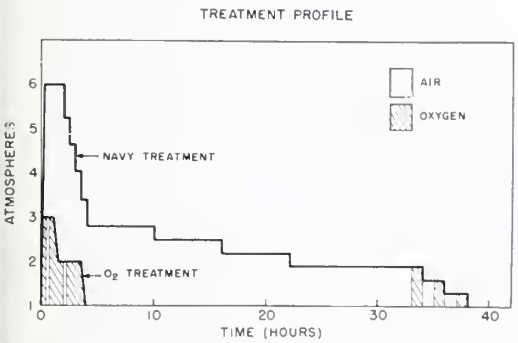

FIG. 11. Comparison of classical U. S. Navy treatment of bends employing compressed air at 6 atms. with newly developed U. S. Navy oxygen method for treatment of bends.

at high pressure and leads to maintenance of a high P_{N_2} in the blood and tissues. The uptake of nitrogen during treatment periods of as long as 48 hours often leads to additional severe bends in the patient or in his physician attendants when decompression is ultimately performed.

Development of the use of pure oxygen at high pressure to treat severe bends and air embolism has drastically reduced the time, the pressure and the equipment required to treat bends (47). Figure 11 compares the treatment profile using oxygen with the classical air method. The use of oxygen at pressures up to 3 atmospheres depends only in part upon the reduction of bubble size by compression itself. Important additional gains are accomplished by a) the rapid *rate of decrease* in bubble size due to the establishment of a maximal outward gradient for nitrogen, and b) establishment of a high gradient of oxygen tension to the regions of impaired circulation. Measures for treating bends were once important only to the diver and caisson worker. If high pressure chambers become extensively used in medicine, oxygen therapy will be required to treat bends generated in the physician as well.

Carbon monoxide poisoning. There is a rational indication for therapy with oxygen at high pressure (22, 40, 44). When our chamber

became available for pressure work in 1947 I arranged with the Director of nearby Philadelphia General Hospital to treat what I expected would be the large number of cases of carbon monoxide poisoning occurring annually in Philadelphia. I learned that severe CO poisoning was extremely rare here, and, as CO itself was eliminated from the household gas system by conversion to natural gas, the number of cases became even fewer and no opportunities presented themselves. However, high pressure oxygen treatment of carbon monoxide poisoning is now extensively used in Scotland (44), where open coal fires and poor ventilation predispose to the intoxication.

Figure 12 shows, for animals exposed to carbon monoxide, the rate of decrease in carboxyhemoglobin saturation during air breathing, its acceleration by oxygen administration at one atmosphere, and the still faster rate of elimination of CO at 2.5 atmospheres (40). This accelerated CO elimination is a result of a dynamic chemical competition of oxygen and CO for hemoglobin. In addition, hyperoxygenation results in an increased pressure head (P_{O_2}) and an increase in tissue oxygen supply in the form of physically dissolved oxygen. At a high enough inspired oxygen pressure (and for a period of time limited in duration by oxygen poisoning) survival should occur even if all hemoglobin molecules are occupied by carbon monoxide.

Radiation therapy of neoplasms. The radiation

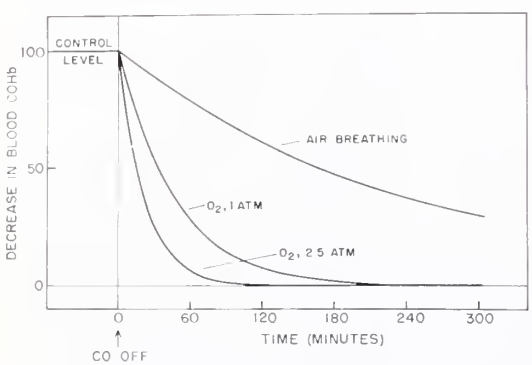

FIG. 12. The effect of increased P_{O_2} on carbon monoxide elimination in men. (Data from Pace, *et al.* (40).)

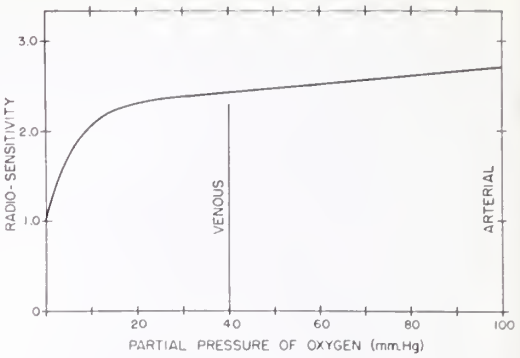

FIG. 13. Alteration of radiosensitivity of plant and animal tissue by change in cellular P_{O_2}. (After Gray (27)).

treatment of certain tumors such as bronchogenic carcinoma has been carried out in patients breathing oxygen at three atmospheres pressure (14, 15). Figure 13 shows the primary basis for combining oxygen and radiation as therapeutic measures. It represents the in vitro sensitivity of various cell types, including yeast, bacteria, plant and animal tumor cells, at different levels of environmental oxygen tension. The figure indicates that sensitivity to ionizing radiation is much reduced at very low oxygen pressures (27). It has been proposed that, as certain tumors outgrow their blood supply, the cells which are most distant from the capillaries become anoxic in vivo and thus resist destruction by radiation at doses which will damage both well oxygenated tumor cells and surrounding normal tissue (14, 15, 27). To restore the relatively anoxic tumor cells to normal radiosensitivity, the patient is exposed to a high oxygen pressure. Under this condition of high pressure oxygenation, radiotherapy is carried out. For the oxygenation of a poorly perfused tissue to be appreciably improved, very high inspired oxygen pressures of at least three or four atmospheres must be used. It should also be noted that the effect of improved oxygenation tends to be limited as oxygen pressure is progressively increased.

High oxygen pressures in coronary disease. Whether hyperbaric oxygenation will find a place in the treatment of acute coronary occlusion in man is now highly uncertain. The

effects of oxygen at one atmosphere in this condition are at last being studied exhaustively (39). Some, but not all, studies in animals indicate that higher than atmospheric pressures provide a significant degree of protection against experimentally induced coronary embolization or ligation (13, 31, 33). However, increased survival was found only when embolization was induced *while* the animal was breathing oxygen at high pressure (33). Thus far no study in man has demonstrated a significant advantage of hyperbaric oxygen therapy in coronary occlusion (48). Oxygen does relieve the pain of myocardial infarction (8) and elevates oxygen tension at the periphery of induced infarcts (43). Coronary occlusion thus remains a defect in tissue oxygenation and means of increasing the known benefits of oxygen administration at sea level should be carefully pursued. Certainly other factors besides oxygenation are involved in a myocardial vascular occlusion. Nutrient, ionic and membranal factors may remain distorted even if oxygenation itself is somewhat improved. The normal heart, an exercising muscle, has its venous oxygen levels only slightly elevated even during exposure to three atmospheres of oxygen pressure. In a region of occluded circulation still less effect should be demonstrable. Prominent handicaps to study and therapy will continue to be the limitations of pressure and duration of continuous exposure imposed by the pulmonary toxicity of oxygen. If gains are made, they will likely result from repeated, programmed, intermittent oxygen exposures at pressures only slightly in excess of one atmosphere, rather than from infrequent, brief, and abortive exposure to extremely high oxygen pressures.

Anaerobic infections. One of the most clearcut indications for high pressure oxygen therapy appears to be in the treatment of gas gangrene (9, 10). Table IV summarizes a number of important features of this fulminating and necrotizing infection. The organism predominantly responsible for necrotizing myositis is *Clostridium perfringens* (Welchii). It is a common part of our environmental flora and

TABLE 4

ANAEROBIC INFECTIONS

GAS GANGRENE
Three species of Clostridia produce most of the clinical infections.
Cl. Perfringens (70%), Cl. Novyi (20-30%), Cl. Septicum (5-10%)
Normal flora of man and his environment.
Disease due to opportunity, not increase in virulence.
Damage is caused by alpha-toxin, a lecithinase, necrotizing, hemolytic, lethal. Fixed in tissues. Fulminating tissue destruction. Toxemia.
Septicemia results in toxin effects in blood. Hemolysis, renal shut-down.
ANAEROBIC CELLULITIS
Not necrotizing.
TETANUS
Fixation of toxin.

becomes dangerous, not through the emergence of especially virulent strains, but when the presence of necrotic tissue and ischemia complicate wound contamination.

Oxygen is an "antibiotic" agent for the anaerobic Clostridial organisms. Exposure of cultures of *Cl. perfringens* to very high oxygen pressures inhibits multiplication of the organisms and can cause their death (9). However, the advantage of high oxygen pressures in the therapy of gas gangrene appears to depend more upon inhibiting formation of the α-toxin, a lecithinase which produces the necrotizing myositis, than upon killing the organisms (9). The toxin apparently is promptly fixed by the local tissues after formation and is not responsible for the severe toxemia of gas gangrene; the decrease in fever and toxemia during oxygen therapy is possibly related to a lessened rate of muscle destruction.

Oxygen administration, even at several atmospheres pressure, cannot be expected to raise cellular oxygen tension or to affect the gas bacillus in regions where the local circulation is not competent. For this obvious reason high oxygen pressure should not be considered a substitute for proper surgical measures including drainage, debridement and amputation. Oxygen, like antibiotic treatment, is only an adjunct to other therapy, but it appears to be an effective and important adjunct. Ways of improving its effect in the necrotizing myositis which is gas gangrene deserves intensive study, as does its possible

role in the less serious forms of anaerobic cellulitis. Thus far there is no clear indication that therapy with high oxygen pressures has a specific effect upon the course of clinical tetanus infections (9, 10).

Other applications. The foregoing are cited as examples of conditions in which high oxygen pressures have been employed in study or treatment. In surgery high oxygen pressures have been employed, with and without hypothermia, to sustain infant or adult patients during repair of cardiac defects (4, 6). Other situations deserving special mention include the general circulatory failure of traumatic shock (18), the decompression, oxygenation and de-gassing of a paralyzed bowel (19), and the treatment of the damaged tissue underlying severe burns. In each of these conditions, the practical application of the evident theoretical advantages of improved tissue oxygenation is distinctly handicapped by the serious problem of oxygen toxicity, which must now be considered.

Oxygen Toxicity

The limits of exposure imposed by oxygen poisoning make it necessary to employ hyperbaric oxygenation on a discontinuous basis. The rate of development of the unfortunate toxicity of a life-sustaining agent, as well as the form it takes, is a function of both the oxygen pressure and the duration of exposure (2).

Pulmonary oxygen poisoning. Two manifestations of oxygen toxicity have particular clinical importance. One is the damage to the respiratory membranes, from nasopharynx to alveoli, which occurs at levels of inspired P_{O_2} too low to produce other demonstrable forms of toxicity (2, 34). This is not surprising since the respiratory epithelium is exposed to a much higher oxygen dose than are the other tissues.

At one third of an atmosphere, equivalent to the 5 psi pressure in the Mercury and Gemini space capsules, it appears that pure oxygen can be breathed for at least a month, or almost indefinitely, without toxic effects (34, 42). In the sea level environment of a hospital, 50 percent oxygen produces no symptoms in 24 hours, but about fifteen to twenty-four hours of continuous pure oxygen breathing causes a moderate degree of chemical pulmonary irritation (17) (Fig. 14). As pressure is raised above one atmosphere the rate of onset of toxicity in animals increases rapidly until at five to seven atmospheres its effects become evident within an hour (2, 15). This phenomenon has not yet been studied in man above one atmosphere.

Central nervous system oxygen toxicity. The second well-recognized form of oxygen toxicity

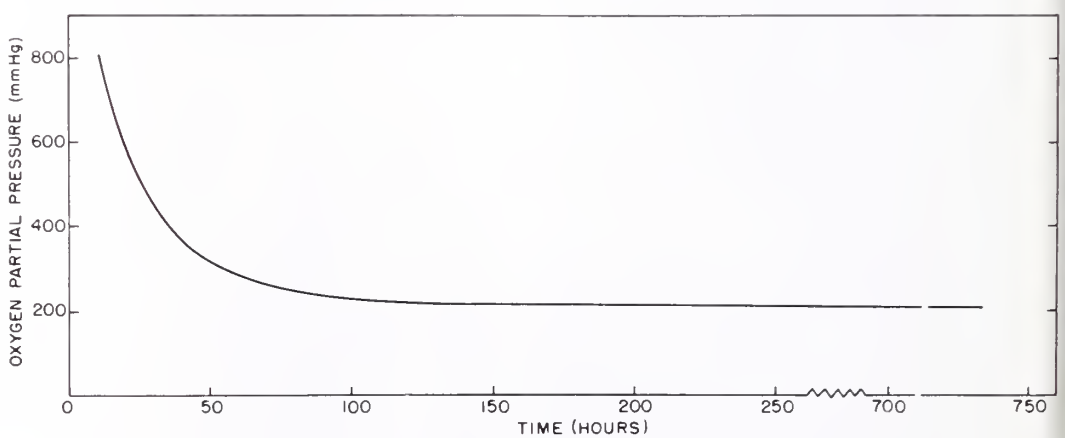

Fig. 14. Tolerance of the lungs to inspired oxygen pressures up to one atmosphere. (After Welch (42, 46)).

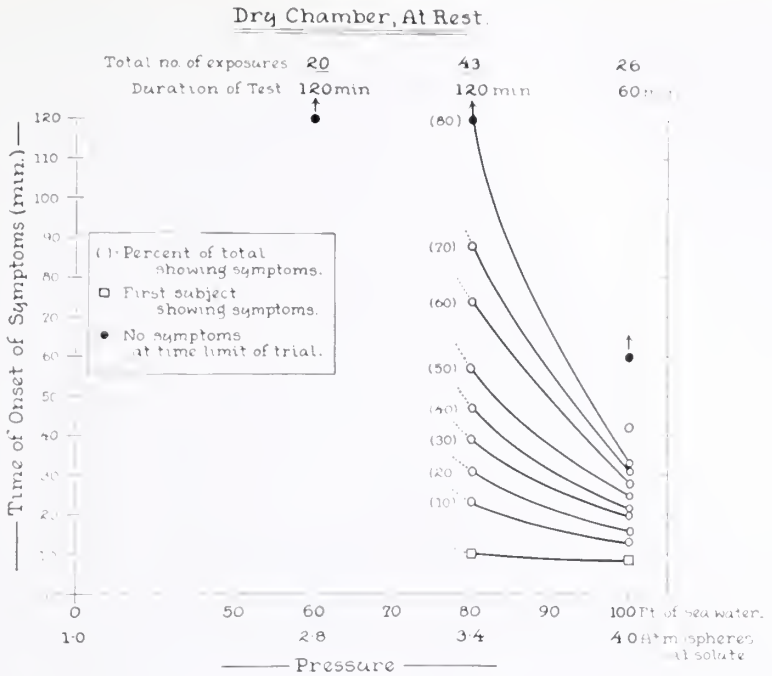

FIG. 15. Tolerance of normal men to pure oxygen at increased ambient pressure. Diagram based upon U.S. Navy studies in World War II (35).

is the generalized, epileptiform, convulsive seizure which results from effects of oxygen upon central neurons (2, 34). At inspired oxygen pressures above three atmospheres, the latent period for development of convulsions in conscious, normal men is shorter than that for production of detectable pulmonary damage, making central nervous system toxicity the limiting factor *in single exposures*. At one atmosphere of inspired oxygen, central nervous system intoxication has not been observed, and pulmonary poisoning limits the duration of exposure. Between these two dose levels, one and three atmospheres, is a region of extreme clinical importance where essentially no information is now available to indicate the duration of tolerance to oxygen of any tissue (34) (Figure 16).

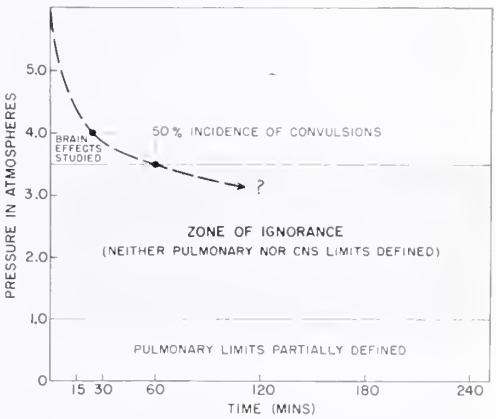

FIG. 16. Tolerance of the brain to high oxygen pressures.

In physically sound men the actual convulsion produced by oxygen is no more dangerous than is an individual epileptic seizure (34). However, the convulsion is a manifestation of the electrical derangements produced by a chemical poisoning. Therefore, if the seizures are ignored or suppressed by drugs such as phenobarbital, it should be recognized that cellular oxygen poisoning will continue and brain damage or death will eventually result (34).

Other forms of oxygen poisoning. As the

effects of oxygen upon man are more extensively studied, evidence of oxygen toxicity may be detected in organs other than the lungs and central nervous system. From evidence of in-vitro studies it is clear that almost any cell, whether plant, animal or microbe, is susceptible to oxygen toxicity and can be expected to be destroyed if the pressure-time dose of oxygen is great enough (16, 26). One unexplained exception to this statement may be the lining cells of the oxygen-secreting swimbladder of deep ocean fish which are exposed to extremely high local oxygen pressures (45).

Due to the great differences in the level of P_{O_2} in various tissues when exposed to a high ambient oxygen pressure (Fig. 7), it is easily conceivable that intolerable oxygen toxicity can be produced in some cells even during failure to relieve anoxia in others (16). For this reason the greatest further gains in application of high oxygen pressures in clinical medicine should come from studies defining and extending the limits of oxygen tolerance.

The biochemical bases for oxygen poisoning. The mechanisms of oxygen poisoning of cell metabolism have been extensively studied for the past twenty years (21, 30). Apparently a high intracellular P_{O_2} can interfere with metabolic processes in several ways. Generally, high oxygen tensions interfere with the oxidation of glucose and with the use of oxygen itself. The effect may well be, at least in part, the result of an excessive rate of oxidation of essential cellular constituents (30). Hyperoxygenation inhibits or inactivates several sulfhydryl containing enzymes concerned with carbohydrate oxidation in the citric acid cycle. It blocks the oxidation of pyruvate and causes its accumulation; this effect may be due to the toxic oxidation of the sulfhydryl-containing substance, CoA. Oxygen also interferes with the formation of high energy phosphate compounds, such as ATP, ADP and AMP, which are important in cell metabolism. In addition to all of the above, high oxygen pressures may inactivate flavine groups of enzymes involved in the electron transport chain (29). With these several sites of oxygen action it is possible that a degree of chemical protection may eventually become feasible. Whether this would aid or negate the beneficial effects of oxygen administration is questionable. At present, prevention of oxygen toxicity at the cell level is no more practical than is the use of drugs to protect against severe radiation damage.

Factors modifying oxygen tolerance. The latent period of central nervous system oxygen poisoning is shortened by muscular exercise and by administration of carbon dioxide during the exposure to high oxygen pressures (2, 34). Drugs which permanently block sulfhydryl enzymes also accelerate the metabolic effects of oxygen toxicity (Haugaard, N., Personal Communication), while sulfhydryl suppliers or protectors of normal sulfhydryl enzymes delay the manifestations of oxygen toxicity (26). The development of oxygen convulsions, but probably not the actual oxygen poisoning, is prevented by barbiturates and other central depressants (21), and should therefore be accelerated by central nervous system stimulants. Cold blooded animals, whose body temperature is kept low, show a much prolonged latent period for oxygen toxicity (2). This and general thermodynamic considerations suggest that in man hypothermia should delay and hyperthermia should accelerate the onset of convulsions.

Intermittent exposure. It has been observed that the rate of recovery from the effects of oxygen toxicity is faster than the rate of development. This finding led to the principle of alternating high and low inspired oxygen pressures to permit greater exposure to increased P_{O_2} within a given period of time without producing oxygen toxicity (35) (Fig. 17). It is hoped that the intermittent, prompt reversal of incipient oxygen poisoning will permit frequent repetition of therapeutic exposures to high oxygen pressure. Although this principle was discovered in man and has been quantitatively demonstrated in animals, the optimal durations of oxygen exposure and interruption of oxygen breathing have not yet been worked out for any pressure in man (34).

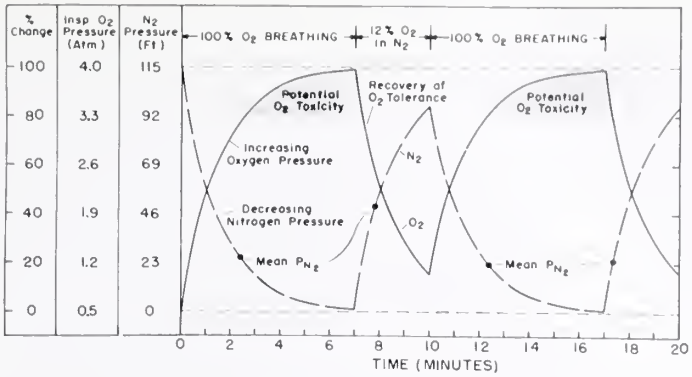

FIG. 17. The use of fluctuating Po_2 in therapy with high oxygen pressures.

PROBLEMS OF DECOMPRESSION AND COMPRESSION

The clinical use of oxygen at pressures above atmospheric pressure involves for the patient and for the attendant many of the same physical and physiological problems faced by the diver. The chamber pressure will ordinarily be increased by compressed *air*, not by oxygen, to avoid what even at one atmosphere would be an extreme risk of explosion or fulminating fire. As the air pressure is raised, the force exerted upon the body surfaces is transmitted uniformly and therefore unperceived throughout all body fluids. Thus, *relative to conditions at sea level*, the pressure of arterial blood in an individual at an ambient pressure of three atmospheres will be over two thousand mm Hg.

Sensations of increasing pressure are normally felt only in the ear, where temporary failure of air to enter the middle ear through the eustachian tube may cause painful inward deformation of the eardrum. Similarly a blocked ostium of a paranasal sinus will result in pain because the increasing absolute pressure in the capillaries and tissues lining the sinus is not balanced by a corresponding increase of air pressure within the blocked sinus. The high pressure gradient from capillary to air space will cause fluid extravasation, capillary rupture and bleeding into the sinus.

At the working pressure, the air breathing attendant may be mildly narcotized by the increased nitrogen tension in his brain. The narcotic effect of nitrogen, barely detectable at three atmospheres, becomes increasingly prominent at higher pressures and can produce unconsciousness at ten atmospheres (12). The oxygen-breathing patient is exposed to oxygen toxicity but, since no nitrogen is accumulated in his tissues during the oxygen administration, he is exposed neither to nitrogen narcosis nor to risk of bends on decompression.

During decompression, gas trapped in body cavities begins to expand, increasing in volume in direct proportion to the decreasing pressure (Fig. 18). The expanding air escapes readily from the middle ear cavity. However, gastrointestinal gas or the air in a pneumothorax at three atmospheres will expand to three times its volume on return to one atmosphere, with potentially disastrous results. Expansion of air trapped in emphysematous bullae may lead to rupture of the bullae and to the development of pneumothorax. Similarly, decompression during breath-holding or with any obstruction to pulmonary ventilation should lead to gross expansion of the intrapulmonic gas, causing rupture of lung tissue and probably massive air embolism.

"Decompression sickness" is a term reserved for the bends. This may occur in individuals who, after breathing air for an extended period of time, decompress too rapidly to allow gradual elimination of the excess nitrogen in the tissues. The rate of nitrogen elimination is circulation-limited and, if rapid return to sea

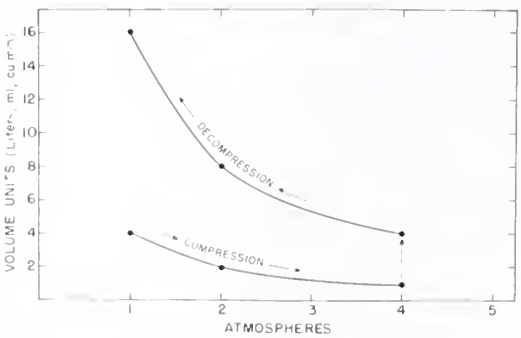

FIG. 18. The effects of pressure changes on gas volumes in body spaces.

level pressure leaves a high partial pressure of nitrogen in a tissue, nitrogen will escape from solution in the tissue fluids to form bubbles. The distortion of tissue and the ischemia produced by the bubbles cause itching, pain, dyspnea or paralysis, depending on whether the bubbles form in the skin, joints, lungs, or central nervous system. Since excess oxygen in the blood is metabolized during one circulation through a tissue, oxygen itself does not produce bends. As pointed out above, if bends due to nitrogen occur in the course of hyperbaric therapy, the most effective treatment is administration of oxygen at increased pressure.

SUMMARY

We have arrived at a reasonable place to end this lecture. It is necessary to sound a strong note of warning that the use of pressure therapy with oxygen is potentially hazardous to patient and physician alike. However, these hazards are subject to logical appraisal in advance and can largely be prevented by awareness of them and by appropriate training of the individuals involved.

Considerable optimism should also be expressed that the use of high oxygen pressures will find a rational and lasting place in therapy. If this prediction is borne out it will be because of meticulous further exploration of the basic effects of high oxygen pressures in normal and pathological states, and on the basis of carefully controlled clinical trials to determine the improvement to be expected with therapy.

In the course of time it is possible that much can be done to extend the therapeutic usefulness of oxygen at high pressures. Of the many avenues which lend themselves to study in man, three appear most deserving of immediate attention. One is the clear definition of the limits of pulmonary oxygen tolerance at rest over a wide range of inspired oxygen pressures. Another is the determination of the most effective schedules for protecting against oxygen toxicity by periodic interruption of exposure to high oxygen pressures. The next is study of the combination of hypothermia and hyperoxygenation for treatment of extreme local hypoxia. Through these and other investigations, opportunity exists for extending not only the practical employment of high oxygen pressures but also understanding of the fundamental principles upon which the ultimately successful therapeutic procedures will be based.

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Immunologic Mechanisms in Glomerulonephritis: Hypersensitivity and Autoimmunity[1]

By ROBERT C. MELLORS, M.D., PH.D.[2]

THE concept that human glomerulonephritis is an immunologically induced disease has been under investigation throughout this century, and I plan to explore, with you, the basis for this enduring and challenging hypothesis. As you know, in 1912 in a monograph on scarlet fever Schick (42) called attention to the latent period of 1–3 weeks between the onset of scarlet fever and postscarlatinal nephritis and, seeing no evidence of renewed bacterial infection, suggested that the nephritis might be due to hypersensitivity, the injurious meeting of bacterial antigens and antibodies in the tissues. The hypersensitivity concept received support from early studies of glomerulonephritis: blood, urine, and nephritic kidneys were usually sterile bacteriologically; and the serum titer of streptococcal antibodies, including antistreptolysin O, was frequently increased. Now of course, it is recognized from epidemiological studies (40) that acute glomerulonephritis is a sequela of pharyngeal infections with a limited number of nephritogenic strains of group A streptococci, more commonly type 12, and that group A infections with other serological types may cause exacerbations of already existing glomerulonephritis.

However, the time-honored view that glomerulonephritis is one disease with varying manifestations divisible into acute, subacute, and chronic stages was challenged in 1942 by Ellis (9) who with his associates at the University of London Hospital studied the natural history of 600 nephritics and concluded that there were two types of glomerulonephritis, for want of a better term called types 1 and 2, differing in cause, course, anatomical lesions, and prognosis. The contrasting but sometimes over-lapping features are well known to you. Abrupt onset, generalized symptoms, history of prior infection, hematuria, edema of short duration, and self-limited course are commonly seen in type 1, or nephritic, glomerulonephritis. The glomerular lesions in the acute stage are mainly proliferative, exudative and hemorrhagic, in the subacute stage crescentic, and in the chronic stage sclerosing. Insidious onset, infrequent or inapparent history of prior infection, nephrotic syndrome, and continuous progressive course characterize type 2, nephrotic, or membranous glomerulonephritis. The glomerular lesions may be minimal in lipoid nephrosis of childhood but in adults, as emphasized by Bell (2) and by Allen (1), usually comprise diffuse thickening and alteration of the glomerular capillary basement membrane and adjacent structures, causing progressive narrowing of capillary lumens but not total obliteration and reduction in number of glomeruli except in the late sclerosing stage when the characteristically large pale kidneys give way to small contracted kidneys with accompanying hypertension and azotemia.

Now of course it is generally recognized that the Ellis classification is somewhat oversimplified and that clinical and pathological overlap and transitions between the two types of glomerulonephritis are seen. In recent years it has also become increasingly clear, especially from the study of very thin sections stained with periodic acid-methenamine silver (21) and the examination of ultrathin sections by electron microscopy (see reference 3), that the intercapillary or mesangial tissue shares the brunt of glomerular injury with the basement

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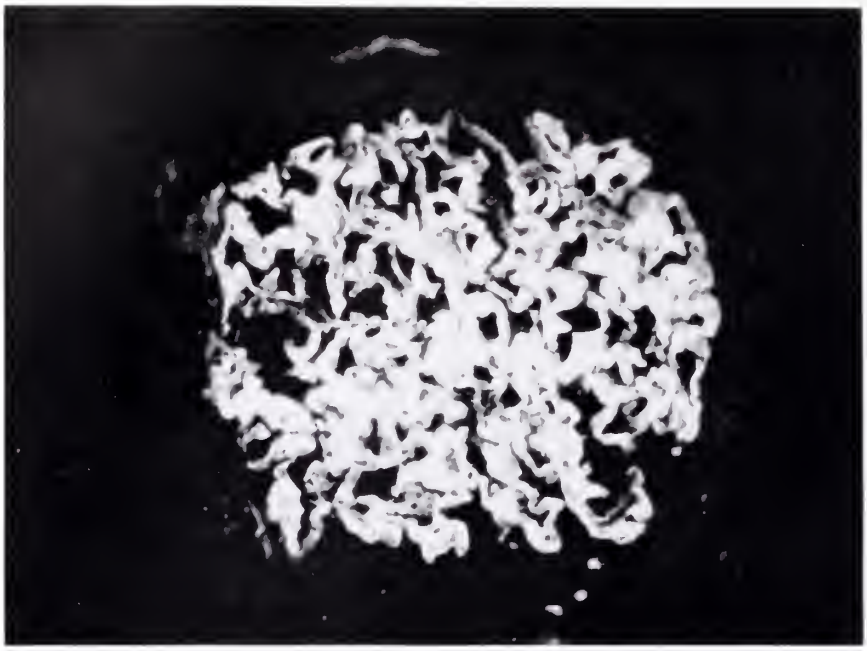

FIG. 1. Human kidney. Chronic membranous glomerulonephritis with γ-globulin localization in diffusely thickened glomerular basement membrane. Frozen section. Immunofluorescence. 340×. (Ref. 35.)

membrane. Moreover the unifying view that immunological mechanisms are in some way connected with the pathogenesis of human glomerulonephritis of either type is suggested by further observations: the serum complement level is decreased in the early nephritic or nephrotic stages (27, 10); antibodies to human kidney are detectable in the serum according to some studies (28); and immunoglobulins (34, 35, 48, 43, 12), Fig. 1, and autologous complement (26, 11) are preferentially localized in the active glomerular lesions in nephritic and nephrotic glomerulonephritis and, one might add, in lupus nephritis. Concerning nephritogenic substances, possibly circulating antibodies, it is notable that human renal transplants even between pairs of identical twins sometimes develop histological lesions characteristic of the antecedent disease of the recipient, glomerulonephritis in one instance and lupus nephritis in another, in the studies of Murray and his associates (37).

Finally three classical examples of immunologically induced experimental nephritis (nephrotoxic nephritis, serum sickness nephritis, and autoimmune nephrosis) resemble human glomerulonephritis in many respects, and most important a newly discovered spontaneous, most probably autoimmune, renal disease of inbred mice (4, 16, 19, 31) appears to be a pathological model of a spectrum of nephrotic renal lesions– lipoid nephrosis, focal ("lupoid") and diffuse membranous glomerulonephritis, and chronic (lobular) glomerulonephritis. It is mainly about these experimental systems and particularly the latter one that I shall speak. Their study further encourages the belief that immunological mechanisms of two kinds, hypersensitivity and autoimmunity, may contribute to the development of human glomerulonephritis.

Nephrotoxic serum nephritis. Early studies of nephrotoxic sera, those produced by injecting an animal of one species with the kidney of another, were undertaken in Europe in 1900 and in this country by Richard M. Pearce (39), Assistant Professor of Pathology at the University of Pennsylvania, who published his first observations in the University Medical Bulletin of 1903–04. However, this early work,

which might well have become a medical classic, lay neglected until the Japanese pathologist Masugi (29) in 1933 demonstrated that diffuse glomerulonephritis could be produced in rabbits by the intravenous injection of duck antiserum to rabbit kidney and that without further measures this immunologically induced renal disease became chronic, causing obliteration of glomeruli by intra- and extracapillary changes such as occur in human glomerulonephritis and resulting in death from renal failure. The nephrotoxic activity of foreign-species antiserum to kidney was shown by Smadel (45) to reside wholly in the γ globulin or antibody fraction. The immunizing or antigenic components of kidney were found, in succession, to be mainly cortical tissue rather than medullary (18), glomeruli rather than tubules, and glomerular capillary basement membrane rather than other structural components (25). Organs rich in capillaries, such as lung (45) and placenta (44), and the kidneys of various species of mammals contain related cross-reacting antigens which elicit the formation of nephrotoxic antibodies. In vivo studies including ours (32, 38) by immunofluorescence, Figs. 2–3, have made it clear that the kidney and within it the glomerular capillary basement membrane is the main and the immediate site of localization of nephrotoxic antibodies. A high concentration of capillary basement membrane antigens (24) with ready accessibility through porous endothelial lining and exposure to a large volume of blood flow at high filtration pressure predisposes to localization of nephrotoxic antibodies—and ensuing tissue damage—in the glomerular tufts. A biphasic reaction occurs, as suggested by Kay (23) and substantiated by our studies (38) with immunofluorescence: immediate localization of nephrotoxic antibodies followed in a few days by glomerular localization of host γ-globulins, presumably antibodies to antigenic foreign globulins. Foreign and autologous γ-globulins persist in the glomeruli in close association for many months, that is, during the acute and the chronic stages of glomerulonephritis.

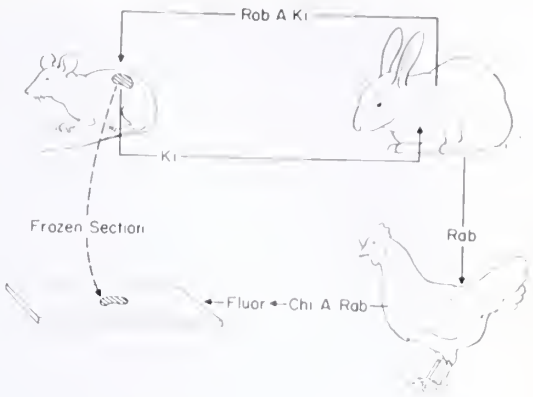

FIG. 2. Original plan for the study of the in-vivo localization of nephrotoxic antibodies by immunofluorescence (Ref. 32).

Experimental serum sickness nephritis, mainly acute and self-limited, is produced with reasonable predictability in the rabbit by the intravenous injection of foreign proteins. Foreign serum, such as horse serum, was used in early studies by Rich and Gregory (41), Ehrich (8), Wissler (50), McLean (30), and others; purified foreign serum proteins by Hawn and Janeway (15), More and Waugh (36), and Germuth (13); and killed bacterial antigens by Wood and White (51), and Feilum and his associates (49).

The studies of Germuth (13) have been pivotal in the understanding of serum sickness nephritis in the rabbit, produced by a single intravenous injection of approximately 500 mg of bovine serum albumin. The glomerular lesions develop after a latent period of a few days apparently at a time when antibody, newly formed in lymphatic tissues, is combining with excess antigen in the interstitial fluid and circulating plasma. As is well known, antigen and antibody combine in the test tube in various molecular proportions; if antibody is in excess, all of the antigen is precipitated; if antigen is in excess, soluble complexes of antigen and antibody appear in the supernatant fluid. Soluble immune complexes of this sort formed by much antigen and little antibody are present for a time in the sera of immunized animals as shown by the studies of Dixon and his associates (5), Sternberger (47),

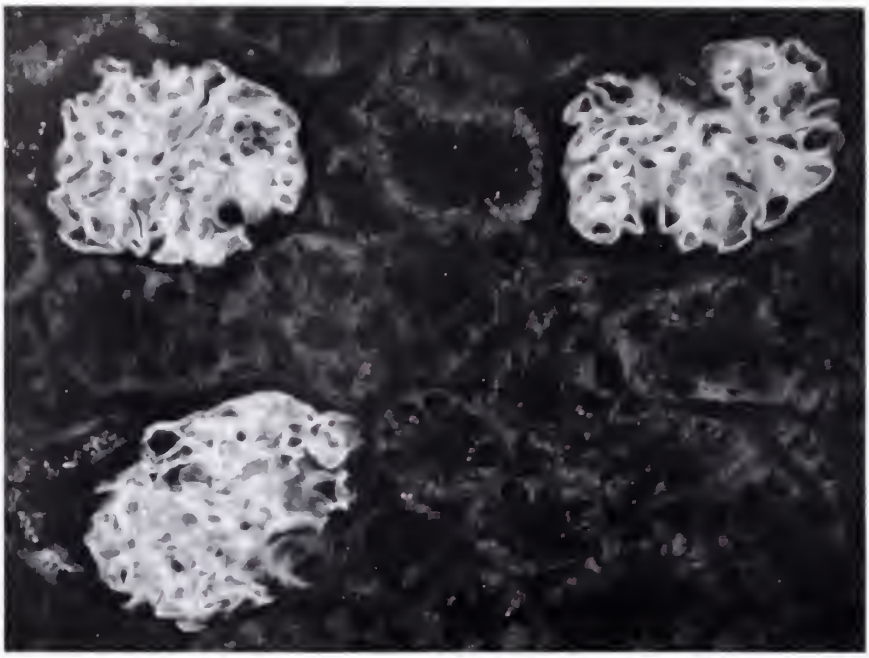

FIG. 3. Mouse kidney. In vivo localization of fluorescent nephrotoxic antibodies in glomerular tufts at 15 minutes after intravenous injection. 425×.

and others. The concept that soluble immune complexes play an important role in the production of allergic lesions of the acute and serum sickness types, including glomerulonephritis, was first clearly expressed by Germuth and McKinnon (14). The toxicity of the soluble complexes was experimentally verified by passive transfer and the production of acute anaphylactic shock. In serum sickness nephritis as shown by our early studies (33), rabbit γ-globulin, presumably antibody, is deposited in the glomerular lesions; and as shown by Dixon and his associates (7, 6) antigen together with rabbit γ-globulin, apparently in the form of circulating immune complexes, is deposited in the glomerular tufts coincident with the development of acute glomerulonephritis. Chronic serum sickness produced by repeated daily intravenous injections of antigen enhances the severity and chronicity of glomerular lesions in some animals (30, 6).

Autoimmune glomerulonephritis. The experimental studies of autoimmunity provide a new approach to the investigation of glomerulonephritis. Heymann and his associates (17) have produced autoimmune nephrosis in rats by immunizing them with homologous kidney suspension mixed in Freund's adjuvant (a water-in-oil emulsion containing killed mycobacteria), and Steblay (46) has produced autoimmune glomerulonephritis in sheep by heteroimmunization with kidney. But the most challenging contemporary model of experimental glomerulonephritis, almost certainly induced by autoimmunity, occurs spontaneously in mice of Bielschowsky's NZB/Bl strain as first reported by Helyer and Howie (16) in New Zealand, studied further by Holmes and Burnet (19) in Australia, and for more than a year under investigation in my laboratory (31). Beginning at 4–6 months and increasing with age, these mice spontaneously develop autoantibodies to their red cells, as shown by positive Coombs' tests, and hemolytic anemia; other autoimmune manifestations; and glomerulonephritis that begins with minimal glomerular lesions and passes through focal ("lupoid" or "wire-loop") and diffuse membranous and chronic lobular and sclerosing stages, that is, a spectrum of intracapillary

structural changes such as seen in human nephrotic renal diseases.

Believing it to be a model immunopathological system, we are studying the NZB Bl mice in breadth, and in depth down to the subcellular and molecular levels of organization. These studies to date may be summarized briefly as follows. Dr. Marriane Bielschowsky kindly sent us a breeding nucleus from the sixtieth generation of her inbred strain of NZB Bl mice. A colony of many hundred has been derived from this stock by brother-sister matings, now in the sixty third generation. Laboratory examinations in several categories (hematology, blood chemistry, urinanalysis, and serology) were performed at monthly intervals. Complete autopsies provided tissues for histopathology, immunofluorescence, and electron microscopy. These studies have shown that membranous glomerulonephritis with spontaneous and insidious onset and chronic progressive course is a major disease of these mice. The earliest and lasting histological changes were hyaline thickening of the capillary walls and adjacent intercapillary regions of the glomerular tufts, corresponding mainly to capillary basement membrane and mesangium when studied by electron microscopy (20). The hyaline materials, stained "soft" pink with eosin, Fig. 4, bright magenta (carbohydrate rich) and somewhat granular with the periodic acid-Schiff reaction, Fig. 5, and black (carbohydrate-rich) and partially fibrillar with the periodic acid-methenamine silver stain, Fig. 6, accumulated focally and diffusely in the glomerular tuft, sparing no glomerulus, and gradually produced narrowing of capillary lumens by concentric or eccentric encroachment upon them. In the later stages hyaline lobulation and hyaline sclerosis of the glomerular tufts occurred. Thus the lesions corresponded to those seen in human focal and diffuse membranous, chronic lobular, and, lastly, sclerosing glomerulonephritis. The focal membranous change resembled the "wire-loop" lesion of lupus nephritis (16) but all animals except one were antinuclear factor negative, and this one only weakly positive. The distribution of hyaline materials was also similar to that of amyloid in glomerular amyloidosis,

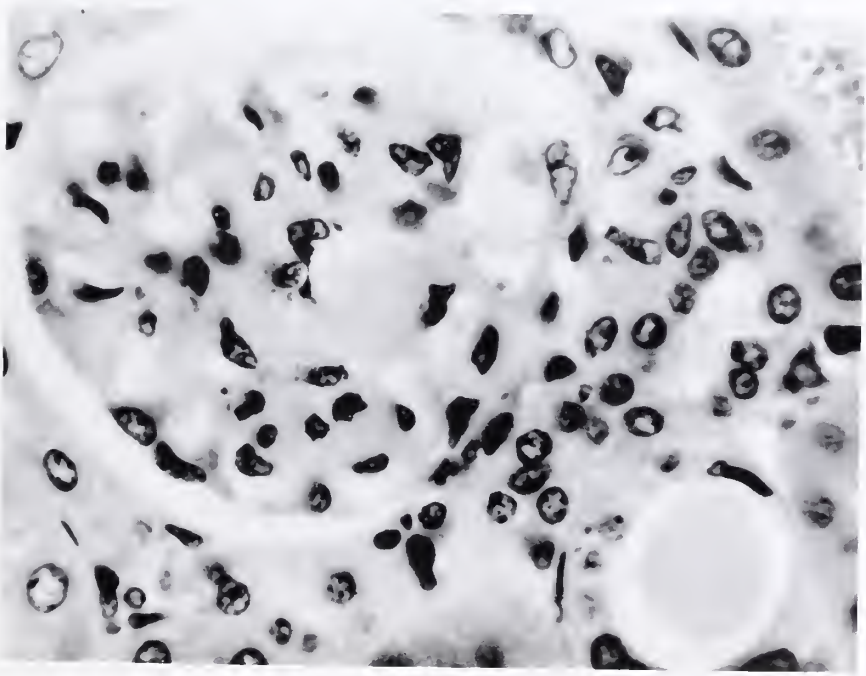

FIG. 4. NZB/Bl mouse kidney. Diffuse membranous glomerulonephritis. Hematoxylin-eosin. 960×

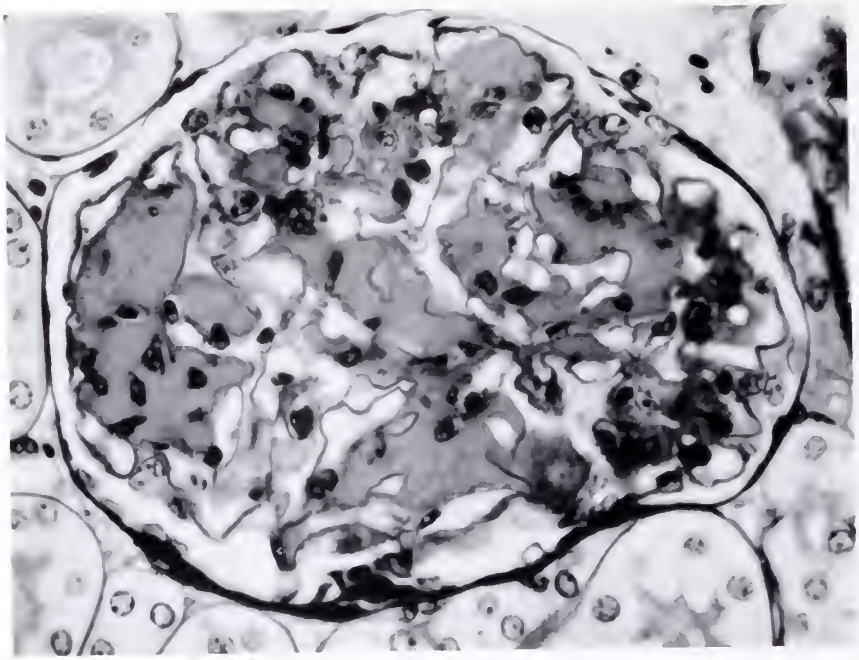

FIG. 5. NZB/Bl mouse kidney. Diffuse membranous and early lobular glomerulonephritis. Periodic acid-Schiff stain. 624×.

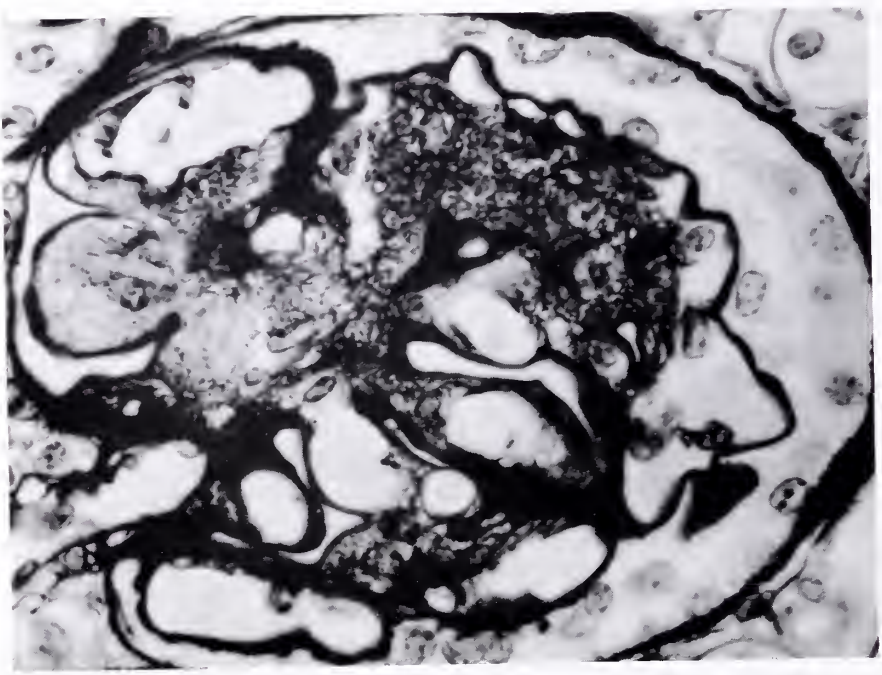

FIG. 6. NZB/Bl mouse kidney. Focally accentuated membranous glomerulonephritis. Periodic acid-methenamine silver stain. 920×.

FIG. 7. NZB/Bl mouse kidney. Glomerulonephritis with γ-globulin localization in glomerular tufts. Frozen section. Immunofluorescence. 424×.

as has been noted (19) but excluded by special stains and ultrastructure (20).

Immunoglobulins were localized in the glomerular lesions, Fig. 7, in all instances, and most abundantly in glomerulonephritis of maximal severity. The immunoglobulins could be eluted from frozen sections of kidney (31) and thereafter had in-vitro affinity for autologous glomerular tufts, that is, displayed the properties of autoantibodies to kidney.

SUMMARY AND CONCLUSIONS

The studies of the last several decades make it clear that glomerulonephritis with close resemblance to the human disease can be initiated and perpetuated in experimental animals by immunological mechanisms. It seems likely that similar mechanisms occur in human glomerulonephritis: immediate hypersensitivity and autoimmunity.

A source of exogenous antigens commonly exists in nephritic glomerulonephritis in a tonsillar or pharyngeal focus of infection with nephritogenic strains of group A streptococci. Gaining entrance into the circulation, nephritogenic antigens may localize in the glomeruli and there react with antibody once it is formed; or antigen and antibody may combine in the circulation to form soluble immune complexes which localize in and damage the glomeruli directly or indirectly as through the action of complement; or antibody to exogenous antigens may cross-react with endogenous antigens, as shown for example by the work of Kaplan (22) with the group A streptococcus and heart tissue.

A probable source of autoantigens is the glomerular basement membrane and related structures which are mainly affected in nephrotic (membranous) glomerulonephritis. Focal and diffuse membranous and chronic lobular glomerulonephritis in NZB/Bl mice are almost certainly manifestations of autoimmunity and provide a model system of spontaneous, insidious, chronic and progressive glomerulonephritis with close resemblance to the human disease.

It seems likely that the concept that

immunologic reactions contribute to the development of human glomerulonephritis will soon become an established reality; and with better understanding new prospects for therapeutic management and prevention will arise.

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Preventive Medicine in Medical Education: an Internist's Viewpoint[1]

By JOHN R. ELLIS, M.B.E., M.D., F.R.C.P.[2]

AN INVITATION to give a lecture named to commemorate a fine man is a great pleasure. I wish to thank the College for giving me that pleasure, and for the honour which goes with it. As one looks at the long and lengthening list of Anders lecturers one realises that with each successive year the honour conferred on each new recipient has grown. It is a formidable array of names which rightly shine in American medicine and on the one previous occasion that a lecturer was sought from across the seas it was my most distinguished and much loved compatriot, the late Sir Geoffrey Jefferson. This lecture, like much good wine, has grown stronger with the years. I fear it may be a little too heady for me.

I was given complete freedom in my choice of subject and I was tempted to choose one about which I, at least, thought I knew something. Instead I chose "Preventive Medicine" about which I know, as you will soon realise, too little. I chose it out of respect for the memory of the work of Dr. Anders, and because, appreciating the importance of Preventive Medicine, I felt that I should accept the challenge and the opportunity to clarify my thoughts about it and about the teaching of it. I took the title "Preventive Medicine and Medical Education" because I would not be so presumptuous as to suggest in the title that I am qualified to speak on the Teaching of Preventive Medicine. I added the words "an internist's view-point" as an explanation rather than an apology for whatever views I might, after due reflection, put forward.

[1] James M. Anders Lecture XXXXIV, The College of Physicians of Philadelphia, 3 March 1965.

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It happened that I began the process of clarifying my thoughts about preventive medicine in a train. My journey took me from the far western tip of the United Kingdom north and east towards London. Thus I travelled through the length of Cornwall, one of the more beautiful parts of the world, a peninsula with one rugged coastline looking defiantly towards America and the other, indented with small harbours and delightful tidal creeks, leaning seductively towards the Continent of Europe. The uplands are bare, glistening with golden gorse: such trees as keep their roots crouch down away from the Atlantic Gales. The valleys are lush. The houses are of granite and cluster in groups each dominated by a church tower, squat and strong enough to have withstood centuries of bad weather.

Here the Cornish, one of the old Celtic races, trading with the Phoenicians and exchanging saints with the Irish, were in touch with the outside world long before the Roman conquest. Here for all the years between, men have fought for their existence and made a hard living from the land, from the sea, and by painfully extracting tin and copper from under the earth. Here mining gave birth to modern engineering, here Richard Trevithick invented the steam engine and paved the way for Brunel to build the line over which I travelled. A line which in a few short hours reveals a panorama of man's efforts at living from prehistoric times to now—a good opportunity it seemed to me to observe our progress in Preventive Medicine.

There was a wide variety of things to see. The bathroom built on—the small hut at the bottom of the garden—the enclosed place for children to play in near the new apartment block. Signs of modern dairy hygiene in an old farm—a bulk milk carrier on the road to the nearest pasteurisation centre—a statue to Sir

Humphrey Davy, the chemist who invented the miner's safety lamp. Nothing much to see about the Davy house, and the eighteenth century front of the biggest hospital, the County Infirmary, did not suggest that the Cornish or the British Government, were putting all their money into modern therapeutic medicine. On most stations a coloured poster illustrating an ashtray full of cigarette ends and the rising incidence of lung cancer denoted concern for health education, and the children outside school drinking their free milk revealed a public interest in the maintainance of good nutrition.

The parish accounts in any of the old churches would, I know, reveal that at least from the time of their origin in the reign of Henry VIII, public money had been expended to succour the bodies and minds of those in need—and in many the obvious little leper's window still bore witness to a long felt dual concern to limit disease and comfort the afflicted. The Church, I decided, in one way or another, had played a big hand in Preventive Medicine; and so had every other institution which played any part in the organisation of Community life. The list in the church porch of those of his relations a man should or should not marry had much the same ultimate aim as the Department of Agriculture's notice depicting a Colorado Beetle.

In one town, through a forest of television aerials, I saw a child, no doubt vaccinated against smallpox and inoculated against diphtheria and polio, invigorated perhaps by its daily ration of petrol fumes, run gaily across a busy street some distance away from a pedestrian crossing. I wondered how much the flashing light of the latter interfered with, or assisted, the sleep of those whose bedroom was so close to it. Elsewhere a man shovelling china clay into a railway wagon was white with dust from head to foot, and so was his face mask hanging on the wall behind him. I decided that the efficiency of our measures to prevent disease depend very much upon the degree to which people believe in them enough to restrict their own liberty by their use. It seems easier to ensure the use of those which impose no limitations on personal freedom. Several cottages showed in their northern windows the gleam of that silver glass ball which the Cornish have used for centuries to keep witches out of the house.

I was wondering how many of my fellow travellers were carrying a potato in their clothes to keep away the rheumatism, or a magnet to keep away cramp in the legs when the train stopped. The elderly lady opposite stood up to alight, and immediately became faint. It appeared however that she was little perturbed by such symptoms, being happy in the knowledge that her "blood pressure" (previously symptomless) was being treated by hypotensive drugs.

I decided that Preventive Medicine in Cornwall and presumably everywhere else is immensely old. Whether originating, as in the past from the ideas and activities of the few at the top, or as now may more often be the case from the ideas and aims of the majority of the masses, it is woven into the fabric of the life of every community. It has been organising medical knowledge for hundreds of years before organised medicine began. It has been motivated by many powerful forces, including the social conscience of individuals and communities, compassion and gain. The community has now assumed more and more of the responsibility and the interaction between the individual and the community is much more complex than it was. Preventive Medicine has always been and is now difficult to define; like the American people it has many origins, and mixed motives, but its long existence cannot be denied, nor can its growing importance.

Essentially Preventive Medicine is the application of measures designed to maintain health, based upon our knowledge of disease and to a smaller extent upon our knowledge of health. Its effectiveness depends upon the extent and accuracy of our knowledge on the one hand, and on the other hand upon our ability to enforce measures which limit the

individual in order to enhance his own or the common good.

Much of the knowledge (correct and incorrect) has been contributed by the medical profession, and more recently science as a whole has made most potent additions, particularly in the field of infectious disease. The measures by which that knowledge has been applied in order to prevent disease are not so dependent on the medical profession. True, doctors have always played and still play a most important role in prevention of disease in the individual, but so far as prevention in the masses is concerned the doctor is but one of many, and perhaps not the most important person involved. What matters most is the power of the community to enforce well informed legislation, and this depends upon many factors such as social structure, community government, the general level of education and respect for law and order.

In any one area, at any one time, the success of Preventive Medicine will surely depend upon the interaction of three variables — the existing knowledge of health and disease, the ability to apply that knowledge and the current incidence of disease. In countries such as the United States and Great Britain, we possess the ability to apply our knowledge and it has been possible to apply a great deal of knowledge, particularly that relating to the causes of communicable disease, but in regard to the now current causes of death (such as coronary artery disease or cancer) and to the main causes of morbidity (such as rheumatoid arthritis or the neuroses) we are faced with such ignorance as to aetiology that we do not know what measures to apply and therefore our ability to enforce them is of small avail. We are forced back on to inherently weak procedures, such as early diagnosis and the limitation of effects of diseases which we cannot prevent. Yet elsewhere, over large areas of the earth's surface, thousands upon thousands suffer or die from conditions about which almost everything is known, but where what is known cannot be applied.

Obviously the essential pre-requisite to effective Preventive Medicine is knowledge about health and disease. Because this knowledge has increased so much in the past quarter century and because there has been such an increase in world communications, it is natural that the world should be acutely aware and ashamed of, troubled and frustrated by the inability to apply existing knowledge in so many places. It is less conscious that in countries such as Britain and America the growth of Preventive Medicine is crippled by lack of knowledge — especially about the aetiology of disease.

With the level of sophistication in the more developed areas being such that people are acquiring a social conscience in relation to the world as a whole, there is a growing demand that diseases which can be prevented should be prevented. Not surprisingly this demand is expressed as "more preventive medicine" with the inevitable inference that doctors should be more actively engaged in preventive medicine than they are. This leads on to the idea that medical students should be made more preventively minded and more preventively effective. No one anywhere in the world will disagree with these aims — but if they are going to be fulfilled it is vital to decide exactly what part in Preventive Medicine in any one country should be played by doctors, for otherwise there is little likelihood that they will ever get properly prepared to play it. No one presumably would ever accept that doctors are or should be solely and wholly responsible for Preventive Medicine.

In my view the doctor has a very special responsibility for preventive medicine in the individual. Admittedly he is greatly limited by the fact that all too often he has to wait for the individual to become ill before he can begin to fulfill this responsibility. This is a limitation which must be reduced but can only be reduced by alterations in the pattern of medical care, and consequently can be effected only very indirectly by medical education. Within the context thus set however, the doctor's ability to maintain health in the individual is directly related to the

nature of his own professional preparation, which must instill into him the necessary attitudes of mind, knowledge and skills. Being preventively minded will not be enough: a great deal of knowledge and expertise will be required also. The knowledge will to some degree relate to disease, but more importantly it will relate to man and to man's needs for health and man's reactions to the causes of disease.

There is nothing debatable about the doctor's responsibility towards preventive medicine for the individual. It is scarcely debatable that he will need help from others who are not doctors if everyone in his country is going to be served efficiently. There are, however, or have been, rather differing views as to how best the doctor can acquire the right attitudes, knowledge and skills—and also as to when he can most profitably do so. Before considering such differences, it is perhaps as well to turn first to the question of what medicine's contribution should be to preventive medicine for the masses, for the community as a whole, rather than for the individual.

Here it seems to me the paramount obligation of medicine is to provide that knowledge of health and disease which is the essential pre-requisite to preventive medicine. Again this is something to which many others besides doctors can and should contribute—but there must be a special responsibility laid upon medicine to define the most important areas of ignorance and ensure that all efforts are directed towards them. The fewer the resources available the more important it is that they should be turned upon problems which are quantitatively of high priority, no matter what emotional appeal less common problems may have.

The second obligation of medicine should, I think, be that of devising the measures by which new knowledge can be applied, and of ensuring that these measures are put into practice. The former calls for the co-ordination of many different disciplines and it demands that some doctors specialise in methods of control—even more than in applying those methods. Ensuring that appropriate action is taken requires something akin to mobilising of the profession so that its maximal influence is brought to bear in the appropriate place. In sophisticated societies the appropriate place is often the public itself, so that the weight of public opinion is the factor which demands legislation. In Britain the campaign by the late Sir Hugh Cairns, the neurosurgeon, to alert the public to the need for motorcyclists to wear crash helmets, is a good example. The efforts of the Royal College of Physicians of London in regard to cigarette smoking are meeting with less rapid success. Always the evidence must be as strong and incontrovertable as possible. In highly developed communities, new preventive measures must cause very considerable interference with the way of life, interest and property of the individual—modern highways or their alternative, a reduction in the number of people allowed to run automobiles, are good examples. Action by government and education of the public are both possible, but both depend on the demonstration of sound evidence. This places a heavy responsibility on the medical profession, and a very heavy burden of work on departments of Preventive Medicine.

In less sophisticated and less highly developed communities, influencing public opinion may be far too slow a process, and a more direct approach to government itself is obviously more likely to produce desirable results at a more desirable speed. In the eighteenth century the Royal College of Physicians of London spent little effort on attempting to alert the public to the dangers of liquor but they persuaded the goverment to make a considerable and highly effective increase in the price of gin.

Preventive measures which, though long since woven into our daily living, are quite new to other countries, require their people to adopt great alterations in long accepted ideas and procedure, some of which had a not unreasonable basis when, in another context (of circumstance and knowledge), they were long ago ingrained as habit. Their too

abrupt dissolution can so disrupt the structure of society that more harm than good results. True the acceptance of new health measures is seldom quick. Much education and much time are needed. Enforcement requires both a respect for the law and an ability to enact the law which do not exist in every country. Nevertheless, once started, the process of breaking down old customs and weakening the hold of old conventions frequently runs on a pace and easily outstrips the ability to establish new and better ways of living. Very careful thought needs to be given not only to what changes should be made but as to how fast they should be made—so that they may create a maximum of advantage with a minimum of undesirable consequences.

In such countries the medical profession has very heavy responsibilities. Extremely well and carefully prepared doctors are needed—who are well in command of modern medicine and who combine great understanding of all aspects of public health with deep knowledge of their own country and peoples. Not always can one expect all these things to be combined in one person, and a close knit team is necessary. The profession, very seldom more than minute in numbers, has to become very clear as to what is the most important contribution it should make. Frequently it is advised to make itself responsible for the application of public health measures—and to fulfill this responsibility by producing as many doctors as possible, who will engage in health education and the application of preventive measures such as have been found successful elsewhere. The provision of some rather general therapy at the same time will, it is suggested, make these doctors more popular and therefore enable them to be more successful educators. The type of preparation advised for these doctors is one which enables them to unleash upon the public the forces of modern therapy, without enabling them to control these forces. Moreover there is the risk that all the intellectual potential available to medicine is absorbed into this compromise type of preparation and few if any doctors are given that very careful upbringing which can enable them to fulfill those responsibilities which should rightly fall upon the profession. In many countries one first class pathologist would be infinitely more valuable than three public health orientated general practitioners. I believe that the problems of preventive medicine in the field, in most countries, demand a vast increase in personnel of many kinds other than doctors, and can be produced far more quickly and easily. Doctors are a slow, expensive, and in the long run probably dangerous way by which to solve so urgent a problem.

I would argue therefore that the responsibilities of medicine to preventive medicine are different in relation to the individual and in relation to the community as a whole. The doctor must be concerned to maintain health in both—but whilst in the individual he must be able to apply his knowledge of preventive medicine, in relation to the community he should primarily aim to provide knowledge which can be applied mainly by others.

I see no great virtue in trying to instruct medical *students* in procedures by which non-medical personnel engage in the prevention of disease. For a long time such instruction was the basis of the teaching of preventive medicine in medical schools. I think it contributed to a lack of interest in the subject. The fact that the teachers themselves never actively engaged in the procedures taught made the situation worse, and put them at a distinct disadvantage by comparison with scientists conducting research and with clinicians engaged in the active care of patients. Moreover the methods of preventive medicine carry an even greater disadvantage—the better they work the more negative is their result. Students, it seems to me, like results which they can see. Perhaps this is why they so often like surgery, and why surgery can be so effective a medium in which to learn how to think clearly and critically for oneself. Prevent tuberculosis completely and there is none to be seen, all that is visible—and that is spread out almost beyond reach of the eyes—are the methods by which prevention was achieved. This is not always an interesting

situation, particularly for any who have never seen the disease. It is difficult to avoid accepting the sad paradox that experience of disease is a necessary incentive to active interest in its prevention—and this fact needs to be taken into account in our timing of the various phases of the teaching of preventive medicine. Tempting though it is to think that we must orientate the student towards prevention from his very first day, I strongly suspect that our efforts to do so may only bore him and we should first allow him to learn about health and the causes and results of its loss. Some I know are not bored—but of these there are some in whom the interest is but temporary and a rather serious reaction against it sets in later. While discussing these general factors which influence the learning of preventive medicine—though not always its teaching, I would like to mention one other. When preventive measures do not work, or do not work well, they may have a serious effect on students to whose attention they are drawn. A kind of nihilism can be engendered. Young people who hitherto have resisted the temptation to regard some conditions as the will of God, begin to do so.

It seems to me that the attitude of mind which it is most important to inculcate is that of an open-minded curiosity as to the aetiology of disease. Such an attitude has not prevailed extensively in medicine hitherto—for several reasons. Medical education tended for a long time to be rather utilitarian, directed mainly at those areas of medicine in which something could be done. The student's attention was concentrated upon the common disorders, and consequently upon diagnosis and treatment, because obviously their very commonness indicated failure to apply any efficient methods of prevention.

There is still opposition to exposing the student to rare rather than common conditions, and some of it comes sometimes from the field of Preventive Medicine. This is strange because common disorders are not necessarily the best nor even the only ones by which to stimulate an insatiable curiosity as to the causes of disease. Any and every variation from normal health, no matter how rare, is important and educationally useful: particularly if it is subjected to enquiry (which may more easily be successful in rarer disorders) into how it came about, how often it occurs and where.

Of course in the past a deep and abiding interest in the origins of disease was somewhat discouraged by the relative paucity of means for prosecuting research into aetiology. Even so it is worth noting that methods were long ago known and used which are still not utilized to the full. Snow's system, for example, of plotting the cholera deaths of 1848 on a large scale map of Soho is one which could, and should, be effectively employed today by many more doctors than it is. ("The Geography of Life and Death": L. Dudley Stamp. Collins, London, 1964.) It would also be a great deal more exciting and useful to students than observing how various public health activities combine in a community to prevent diseases which he has never seen. These are activities in which he will never be likely to be seriously interested until as a young doctor he is actually working in a community. As a student, however, he can plot out the incidence in a community of various kinds of accident of industrial disease and even of infection.

Now that the advances of Science have sharpened our power to investigate both the nature of health and the causes of its loss, it should be possible for students to become involved in the search for knowledge; thereby acquiring existing knowledge, a sense of curiosity and the power to put it to good purpose all at the same time.

If we set out to inculcate curiosity, and there will be little hope for preventive medicine if we do not, then we must also set out to enable the student to satisfy it—otherwise he will merely be doomed to frustration. The doctors of the future must be able to work under conditions which allow them to engage in effective enquiry rather than idle speculation and so they must, as students, acquire that scientific method of thought which is essential to critical investigation.

Scientific method of thought cannot be ex-

pected to be an automatic result of much reading or didactic teaching. It will not be an inevitable accompaniment of great knowledge, though it can confer the power to acquire knowledge. It will not necessarily arise out of experience, though it makes it possible for one to profit from experience. Scientific method of thought, unlike scientific knowledge, needs its own methods of education, which depend greatly on learning by doing and necessitate an opportunity to study at least one subject in considerable depth. For this reason the preparation of a modern doctor must include a university education in medicine in which the arrangement and the content are relevant to learning, rather than to future practise. This in its turn means that much vocational knowledge and skill must be left to periods of in-service training which are completed after graduation.

Such a two or three stage preparation seems to me essential if the doctors of tomorrow are to be properly orientated towards preventive medicine, and adequately prepared to make those contributions to it which are urgently needed. The department of Preventive Medicine must be fully engaged in each of the stages. The subject itself provides admirable media (such as epidemiology) in which to learn scientific method of thought in the University stage, provided of course that previous education has given the necessary basis of mathematics and statistics. The subject also provides excellent media in which the young doctor can learn about the community by participating in its care.

Fortunately this same scientific method of thought is now vital to purely therapeutic medicine. With it, armed also with sound clinical method, the doctor can apply modern medicine with safety, maximum efficiency, and maximum kindness. He can also keep abreast of change in medicine by critically evaluating new ideas and new data. Without a scientific method of thought, even if he has sound clinical technique, he can do no more in safety than repeat such procedures as he once uncomprehendingly mastered. In a sense therefore scientific method of thought is the very force which enables the therapist to give aid without creating disease for almost every modern remedy carries danger to the patient, and so do many diagnostic procedures. Only the most critical and ongoing analysis of many variables can confer the maximum benefit of modern medicine with a minimum of risk. Only the surgeon who performs his task with his own hands at a carefully prearranged time in front of expert witnesses has "built in" safeguards. The internist's new powers can be invoked by merely writing a prescription, and his patient is safeguarded only by the degree to which he makes a critical assessment of all the data which he has amassed. The modern doctor by acts of commission or of omission is potentially one of the most powerful causes of disease.

It is sad that there should ever have been an idea that scientific method of thought conflicts with the needs of prevention, but possibly it is not surprising. The management of every patient is an exercise not only in the treatment of disease but also in the prevention of later trouble in that patient, in his family and in his community. Perhaps it was natural that the greatly increased power of treatment in the last quarter century should have led to anxiety that the element of treatment would squeeze out the element of prevention. After all, for 100 years medicine had used science without seeing any need for doctors to be scientifically minded. Students were taught and doctors used the results of science without any real awareness of how these results were achieved or upon what they depended. The products of science were applied precisely as the heritage of purely empirical knowledge was applied, except that the former were frequently thought to be in some odd way more cold and less humanitarian.

It was not surprising that as science began to contribute more and more, men who themselves were not scientifically minded began to fear that students would, by learning more scientific therapy, become more impersonal to their patients, and less "preventively minded". It was not unnatural that the cry for 'Comprehensive Medicine" began to be heard, in-

ferring that this was some kind of preferable alternative to Scientific Medicine. Many a department of Preventive Medicine set out in good faith, and with some sense of urgency, on the difficult road of teaching a holistic attitude towards the care of patients, none of whom unfortunately were actually under their care. Surely, however, it is now clear that scientific medicine demands that all factors, all variables, physical, chemical, psychological and social, must be taken into account in every condition. Empirical medicine (which may employ the results of science) can, and too often does, concern itself with disease, but scientific medicine applied by a man who can think scientifically must by its very nature concern itself with the patient, and with all of which he is a part. George Packer Berry put this so much more succinctly over a decade ago when he said, "Scientific Medicine must become comprehensive medicine, yet not become thereby any less scientific". ("Preventive Medicine in Medical Schools", Association of American Medical Colleges, 1953.) I think when those words were said what we were calling Scientific Medicine was not sufficiently comprehensive, and there was a need for Departments of Preventive Medicine to make the efforts they did. Since then however, Scientific Medicine, by becoming more scientifically minded has become more comprehensive, and adopts a holistic approach to the patient. Where in any particular medical school this is not the case, the remedy must at least partially lie in creating a more, rather than a less, scientific attitude of mind among clinical teachers.

I would claim therefore that the first thing required of Medical Education by Preventive Medicine is the inculcation of curiosity about the actiology of disease; the second thing is the scientific method of thought by which that curiosity can be put to good use, which will at the same time (if accompanied by sound clinical technique) ensure satisfactory therapeutic and preventive care of the individual patient. The third thing is the inculcation of what might be described as a quantitative approach to everything in medicine. This of course depends in turn upon techniques such as those used in epidemiology, and upon a facility with mathematics and statistics. But it is not enough for the student to possess those methods, he must also acquire entrenched habits of using them. Therefore he must be encouraged throughout his time at medical school to look at everything quantitatively. He must be got into the habit of subjecting everything he does in medicine, and everything his teachers do, to a critical and quantitative appraisal.

This has not been greatly encouraged in medical schools in the past, again partly because the relevant techniques were too poorly developed but also partly because we were more concerned to teach what was done, than we were to decide how much, or how little, it was worth doing. Now that students are less easily able to participate in the care of patients they welcome the opportunity to participate in evaluating the care given by others. Having done so they become more inclined and better able to assess their own therapy when as interns and residents they begin to give it.

So much for attitudes of mind and methods of thought. Those which are needed for Preventive Medicine do not seem to me to conflict in any way with those now needed for Therapeutic Medicine. The same I think applies very largely to knowledge and skills. Prevention and therapy both depend upon an understanding of man as a complex but indivisible unity of mind and body, who develops as an individual within a family and community. Both require knowledge, much more than we now possess, of the factors necessary to the maintenance of his health, whether these be nutritional or psychological or anything else. I wonder what the optimum temperature and humidity of the air in a living room really are. I'm sure they are not to be found in an English home nor even in an American one. Prevention and therapy both require knowledge of all adverse factors which threaten health and of man's reaction to these. There can be no question of subdividing knowledge, or skills for that matter, into that which belongs to preventive and that which belongs to therapeutic med-

icine and our teaching must never be conducive to such a separation. Our main endeavour must surely be to ensure that both are presented together to the student, but at the most appropriate time and in the most appropriate way. Timing is, I believe, of vital importance and knowledge must be presented to the student at the time when he has the best motivation for assimilating it, and when his earlier knowledge and skill enables him to do so. We must not force specific knowledge and specific techniques of prevention or anything else, into the medical school curriculum just for the sake of coverage or in the hope of controlling attitudes. At the moment, I believe we do, and require in consequence important data to be handled by instruction in the abstract or within some artificially contrived situation. We should allow these things to follow (not precede or even always coincide with) experience in the care of sick people. This should arise out of the problems of individuals or from participation in the care of communities. Just as much of modern therapy can only be learned by participation in it and therefore belongs to internship and later, so much of modern prevention must also be incorporated into this stage of training. Moreover, as no one can be expected to acquire all knowledge and all skills there should be no attempt to teach them all—but a successful attempt must be made to ensure that each young doctor acquires all the knowledge and skill relevant to the branch of medicine which *he* is going to practise.

I am sure that we should reconsider the teaching duties of the Department of Preventive Medicine towards the intern and the resident. Existing lack of University control over these increasingly important stages of medical education cannot always remain an excuse for relative inaction. Internship provides or should provide, the best if not the first experience in the care of sick individuals. The intern really becomes aware of the patient as a member of a family and of a community. This, and just after it, is the time when he is, in my experience, deeply concerned to learn all he can about the inter-relationships of the medical and health team, and begins to be concerned with the practical realities and applications of preventive medicine.

I believe that somewhere early in the Residency period there should be, for most doctors, a required experience of participating in community medicine. I believe it should be preceded, or at least supported by, formal education organised by the department of preventive medicine. This, I appreciate, will throw a great strain upon these departments, but in return they ought now to be relieved of many of the efforts they have had to make for clinical students. They should no longer have to make the same contribution to teaching the student how to fulfill a holistic approach to the patient. They should be allowed to escape from the invidious position of trying to get dividends out of talking in the abstract about the care of communities while the student is heavily engaged in and rightly concentrating upon learning how to understand the nature of disease in the individual.

I believe a Department of Preventive Medicine is essential to a University medical school. I accept the outline of its functions given by Berfeustam of Uppsala: "The functions include much more than imparting a certain amount of practical knowledge and coordinating existing knowledge. They comprise also the creation and dissemination of a new body of knowledge, which is necessary both for the guidance of medical thought and for medical practice. In addition, there is the important though difficult and positive function of the catalyst—attempting to influence teachers in every branch of medicine in such a way that the sociomedical aspects of their teaching are always kept in mind. The duties of the department should also include presenting and sharpening tools of investigation and assessment not often used heretofore by physicians and medical students but familiar to paramedical sciences such as sociology and psychology." (Berfeustam R., in "Preparation of the Physician for General Practice", Public Health Papers. W.H.O. Geneva, 1963).

You must allow one the privilege of draw

ing your attention to an outstanding example of how a Professor of Preventive Medicine has sharpened tools of assessment. John Hubbard's contribution to examining techniques has provided the basis of what can be called a breakthrough in medical education.

I think only a strong department can fulfill the functions outlined by Berfeustam. The department must also be large, for it must combine the expertise of several different disciplines and the knowledge of several different subjects. It must, in my view, have access to graduate doctors in training, as well as to medical students.

I realise that I have dealt with extremely important and complex issues in a very superficial manner. I have deliberately concerned myself more with educational objectives than with educational method or the curriculum. This is because I think methods must be contingent upon objectives, and because I think the curriculum must be something which is "personal" to each school of medicine. An abstract curriculum has no reality whatever. The making up of such curricula is in fact a dangerous pastime. We are so accustomed to think only in terms of the years at medical school, that the curriculum game still continues to be played as though the whole of medical education had still to be squeezed into those few years. Even more serious is the tendency to think of abstract curricula in terms of the number of hours to be devoted to a particular subject. Such estimates are often harmful for they encourage a tendency to think in terms of departmental claims on students' time, and unfortunately evoke ideas of departmental status. They discourage the tendency to think in terms of a departmental contribution to the needs of the student. (Ellis, J. R.: The Teaching of Psychiatry, B.M.J. *ii*, 1963).

I do not believe that the teaching of Preventive Medicine can be improved merely by increasing the time now devoted to it in the medical school curriculum. Indeed, the demand for more time can defeat its own object, for it implies a separateness between preventive and therapeutic medicine which is very undesirable. In the medical school years attitudes and methods of thought are more important educational objectives than are knowledge and skill. The attitudes engendered towards Preventive Medicine depend as much upon all the clinical teachers as upon the teachers of Preventive Medicine. Therefore greater success in teaching the subject can never be achieved simply by increasing the time allotted to the department, and must depend greatly on the influence of that department on all others.

I am aware that in many quarters it is felt that medical schools in both Britain and America are failing to orientate their students properly towards preventive medicine. I find myself wondering whether this is really the case, or whether it is that people think it must be, simply because the students spend so much more time with what are considered therapeutic departments than they do with those unconcerned with therapy.

If it is really true, then I suggest that there can only be a limited number of reasons. Either we are teaching the wrong things in Preventive Medicine: or the right things are being taught by the wrong people: or the right people are teaching the right things but at the wrong stage of student growth: or we are teaching the wrong kind of student: or some combination of all these possibilities. We ought to try to find out—but until we know for certain we must use, as doctors always have to use, our clinical judgement. Mine tells me that our greatest failure is our inability to offer opportunities for learning the knowledge and technique of preventive medicine at the time when this would be most acceptable—internship and residency.

Of course judgement, even when one has tried to make the most critical analysis of the data, is always affected by personal experience. I am very conscious that I have had certain experiences which have greatly influenced my thinking about the teaching of Preventive Medicine.

My first clinical teacher was Donald Hunter whose contributions to industrial medicine are world famous. I was totally unaware of that

when I was his student. I was however aware that there was a man who combined the greatest possible interest in all aspects relating to the individual patient with a live and active concern for people in the mass—one whose enthusiastic curiosity about the aetiology of disease was catching—one who combined an abiding love of the past with a passionate concern for the future. I knew him only as a clinical teacher—even when he took us through the sewers of London.

The second experience which influenced me was during the war when I was a ship's doctor. Hygiene, physical and mental welfare of 400 men became reality for me—and as censor I read the letters of the 400 and in consequence received an education which I do not know how to parallel in modern life.

Finally, through an interest in medical education, I have been privileged to meet, talk and think with more doctors from the field of Preventive Medicine than would otherwise ever have fallen to my lot. Some of them are here today—and I would like to conclude by expressing my gratitude to them for what they have done to me—and my awareness of the fact that very obviously there is a need yet for them to do much more.

The Woman's Medical College of Pennsylvania[1]

By CATHARINE MACFARLANE, M.D.[2]

THE Woman's Medical College of Pennsylvania will be one hundred and fifteen years old this year. It was the twenty-fifth medical college to be established in this country and confirms the truth of Galileo's discovery that the world moves.

One hundred and eighteen years ago, in this "Land of the Free and Home of the Brave", women were second-class citizens. Women could pay taxes but they could not vote. They certainly could not study medicine. The women, however, did not see it that way.

In 1847, Elizabeth Blackwell, a young English woman whose family had moved to Cincinnati, Ohio, decided that she wanted to study medicine. She applied for admission to the four medical schools then in Philadelphia and was refused because she was a woman. She was advised to apply for admission to a small medical college at Geneva, New York. The Dean and Faculty had no desire to admit a woman, but for some reason hesitated to go on record to this effect. They decided to submit the matter to the student body, confident that the young men would vote in favor of turning the application down. Instead these chivalrous young men voted unanimously—one hundred and thirty strong—in favor of admitting the young lady and sent her a very nice letter to that effect.

She entered the Geneva Medical College five weeks late but soon caught up with the class and two years later, in 1849, graduated with honors. She was the first woman to receive the degree of Doctor of Medicine in this country, in fact in the entire Western Hemisphere. The Faculty then voted not to admit women students!

[1] Read before the Section on Medical History, The College of Physicians of Philadelphia, 9 February 1965.

[2] Research Professor of Gynecology, The Woman's Medical College of Pennsylvania, Philadelphia, Pennsylvania 19129.

Impressed by the epoch-making event, some Quaker physicians in Montgomery County, Pennsylvania, Dr. Hiram Corson, Dr. Bartholomew Fussell, and Dr. Joseph Longshore, decided that if their sisters ever wanted to study medicine they had a perfect right to do so, and that they would make this possible. A charter was obtained from Harrisburg for the "Female Medical College of Pennsylvania". A group of public spirited men formed a Board of Incorporators. Three rooms were found in the rear of a building at Third and Arch Streets. Mr. William J. Mullen, President of the Board of Corporators and champion of unpopular causes, paid the rent. Six physicians braved the disapproval of the Philadelphia County Medical Society to form the Faculty. Forty young women applied for admission; some because they really wanted to be physicians, others because they wanted to learn something about their own anatomy and physiology. On October 12, 1850, the College opened. Two years later, in 1852, eight young women were graduated.

One of the first graduates was Hannah Longshore, a young Quaker lady. She opened an office in the center of the city. She had a horse and carriage and drove at high speed through the city streets as if on the way to a very sick patient. She complained that the druggists were prejudiced and would not fill her prescriptions. The druggists said the prescriptions could not be filled because the drugs prescribed were incompatible.

Ann Preston, another member of the first class, was also a Quaker but cast in a gentler mould. More than one hundred years ago, she realized the importance of bedside instruction. She succeeded in interesting some prominent women. In 1861, a charter was obtained to establish "a hospital for the diseases of women and children with facilities for the clinical instruction of women in medicine and for the

practical training of nurses". A house was rented on North College Avenue, then on the outskirts of the city. There the Woman's Hospital of Philadelphia began.

The College, meanwhile, was in grave financial difficulties. In 1861, there was only one woman in the graduating class. In 1862, the rooms at Third and Arch were abandoned. The College rented rooms from the Woman's Hospital and reopened with twenty students. In 1866, Dr. Ann Preston became Dean.

Also in 1866, Rebecca Cole, the country's second negro woman physician was graduated.

In 1869, Dr. Clara Swain, the world's first woman medical missionary was graduated. At first the Mission Board of the Methodist Church was unwilling to send her to India because she was not married. Eventually they overlooked that detail and she was able to realize her life's ambition. In the land of "Purdah", she did untold good. Finally she was so helpful to the sister of the local maharajah that he gave her an elephant complete with huldah and driver so that she might visit her patients in proper style.

Brigham Young sent a young woman from Utah to the College. While in Philadelphia she had to support herself. In a museum in Salt Lake City, there is a picture of this young woman with her baby on one arm and on the other some towels that she was trying to sell during the summer vacation.

In 1875, with the help of some wealthy Quakers, the "New College Building" was erected on North College Avenue, in the same block as the Woman's Hospital and in close cooperation with it. All went well for twenty years.

In 1886, Ananhaibai Joshee, the first Indian woman to receive a medical degree was graduated from the College. She returned to India, contracted tuberculosis and died after five years.

In 1889, the first American Indian woman—Susan LaFleche—was graduated. Her father was Joseph LaFleche—"Iron Eye Chief" of the Omaha tribe.

In 1894, the second Chinese woman to become a physician—Hu King Eng—was graduated.

In 1886, Clara Marshall, a member of the Class of 1875, became the fourth Dean of the College. She was a member of a prominent Quaker family. She had many wealthy patients and contacts with important people in the city. She was the first woman to serve on the staff of the Philadelphia General Hospital.

In 1892, the American Medical Association launched a program to improve the standards of medical education in this country. One of the requirements was that an "acceptable medical school must have a hospital controlled by its Faculty".

Since the Managers of the Woman's Hospital were unwilling to relinquish control of their Hospital, it became necessary for the College to build one. The Faculty decided that the hospital must adjoin the College. It was eventually built on North College Avenue on ground between the College and the Woman's Hospital. This was not popular with the friends of the Woman's Hospital.

In 1917 Dr. Marshall retired and was succeeded by Dr. Martha Tracy of the Class of 1904. Dr. Tracy was a charming woman and a distinguished scholar. She had taught in the departments of chemistry and preventive medicine before becoming Dean of the College. On her watch chain she wore nine Phi Beta Kappa keys that had belonged to various members of her family. One of her ancestors was Roger Sherman, Connecticut's delegate to the Continental Congress who had signed all four documents that contributed to the birth of our Nation—the Declaration of Independence, the Articles of Federation, the Constitution and the Bill of Rights.

Dr. Tracy's friend and associate, Dr. Ellen C. Potter, headed the College Hospital. These two women succeeded in interesting two important people in the College. One was Mrs. James Starr—Sara Logan Wister Starr—a descendant of James Logan, the Quaker school teacher who came from England as William Penn's secretary and eventually became President of the Council of the Commonwealth of Pennsylva-

nia. The other was Walter Lee Sheppard, one of Philadelphia's leading lawyers.

Mrs. Starr took her responsibilities as a corporator very seriously and was soon made President of the Board.

In 1921, both College and Hospital were in debt. Mrs. Starr and Mr. Sheppard advanced fifteen thousand dollars to pay these debts provided the Faculty and Staff would accept centralized control. Among other things, centralized control included limiting the number of entrances to the Hospital, thereby reducing the number of door attendants to be paid.

Some members of the Staff, accustomed to going in and out when they pleased, resented this ruling and refused to comply. One member of the Faculty was not reappointed. Others resigned. All but three of the students went out on a sympathy strike. The continuing Faculty lectured to practically empty benches.

Soon the students returned. New faculty members were found. All went on as before. Meanwhile, the forty-nine year old building had deteriorated. The neighborhood at North College Avenue had deteriorated—it was no longer safe for young women to return there late at night. It was decided, therefore, to move. On the advice of a real estate friend of Mrs. Starr, nine acres were purchased on Henry Avenue on "high ground overlooking the Schuylkill River" where Alexander Hamilton had wanted the Capitol of the United States to be built.

On June 12, 1929, ground was broken for the present College building. A troop of East Falls children arrived with band and banners ready for the anticipated ice cream cones. These being delayed, the children became restless. To quiet them, Mrs. Starr asked, "Can you children say the Lord's Prayer?" 'Oh yes,' was the reply, and with folded hands and bowed heads, they repeated the beautiful words. So the ground was consecrated by the prayers of little children and Dr. Margaret Butler proceeded with her address.

To date 2793 women have graduated from the Woman's Medical College. Our graduates now comprise 6 per cent of the women physicians of this country.

Many followed Clara Swain to the mission field. Dr. Elizabeth Reifsnyder, 1881, established a hospital and medical college for women in Shanghai, China. She established her reputation as a surgeon by removing an ovarian cyst containing twenty-two quarts of fluid while the patient's friends waited outside ready to slay her if the patient died!

Dr. Rosetta Sherwood Hall went to Corea and established a hospital and medical college for women in Seoul. In recognition of her twenty-five years of devoted service, the Emperor of Corea presented her with a ceremonial tea set which her family generously gave to the College. A few years ago, a distinguished visitor from Corea on seeing this service, exclaimed, "That is priceless," not in dollars and cents merely, but because there probably would never be another Emperor of Corea.

Dr. Ida Scudder of India spent two years at the College, then left to complete her medical education at Cornell because the College Hospital then had no men patients. Her niece, Dr. Ida B. Scudder, graduated from the College in 1919 and now heads the Department of Radiology at Vellore Medical College.

Saniyeh Habboub, the first Syrian woman to study medicine, graduated here in 1931. She left her home in Beirut properly veiled but discarded her veil at Marseilles, realizing that she would be more conspicuous with it than without. On reaching New York, she had only one address—the Young Women's Christian Association. It was a hot summer day and the women of downtown New York were rather scantily dressed. She decided the taxi was taking her to a "Bad House". Only upon seeing the sign over the door did she relax. With hard work and the help of her classmates, she graduated from the College in 1931.

Marion Bottomley Hall, Dr. Sherwood Hall's daughter-in-law, worked for many years at Ajmer, India. In addition to her regular hospital work she conducted wayside clinics and gave much needed instruction in family planning.

Recently two of our graduates were in the Congo—Dr. Theodora Johnson and Dr. Frances Stuart. Fortunately both escaped alive. On furlough a few years ago, Dr. Johnson exclaimed, "I wish someone would invent a tasteless quinine that my malarial children would not spit up."

Dr. Honoria Acosta Sison, 1909, was head of the Department of Obstetrics and Gynecology at the University of the Philippines for many years.

Here at home our graduates have made good in all fields of medicine—general practice, many specialties, research, psychiatry, war work, public health and preventive medicine.

During Governor Pinchot's administration, Dr. Ellen C. Potter was Secretary of Health of the Commonwealth of Pennsylvania. The Governor referred to her as "the best man in my Cabinet".

For eighteen years, Dr. Harriet L. Hartley was head of the Department of Child Hygiene in the City of Philadelphia, as well as Professor of Preventive Medicine at Temple University.

For many years, Dr. Lillian South was head of the Department of Child Hygiene of the State of Kentucky.

Dr. Rosalie Slaughter Morton did distinguished war work in France and Serbia during World War One.

Dr. Katharine Boucot Sturgis' work in diseases of the chest—tuberculosis and cancer—is known throughout the world.

Today, 217 young women are enrolled as students in the College. They represent fifteen states of the Union, the District of Columbia, and three foreign countries—China, Indonesia, and Iran. Year after year, some forty or more young women are graduated. They make a real contribution to the relief of the physician shortage that plagues the world today. For the past twenty-one years under the leadership of Dr. Marion Fay, the high standards of the College have been maintained. We anticipate the same distinguished leadership from her successor, Dr. Glen R. Leymaster.

In closing, I will quote the words of Mrs. James Starr to a group of students: "The College is a Temple of Learning. You are the stream passing through."

Ann Preston: Dean of The Woman's Medical College of Pennsylvania, 1866-1872[1]

By MARION S. FAY, PH.D.[2]

THE 1830's and '40's and '50's were important decades for the women of the United States. Anti-slavery was a burning issue and many women became ardent advocates of abolition. They became such forceful speakers that they gained permission to speak from public platforms. As they spoke against slavery of the Negro, they began to speak and think about the position of women. The women's rights movement grew out of this and the first convention to discuss women's suffrage was held in 1848 at Seneca Falls, New York.

Ann Preston lived in this exciting age. She was born in West Grove, Chester County, in 1813 to a family of birthright Quakers. West Grove was not an isolated small town; the Prestons and their Quaker and non-Quaker friends joined the Anti-slavery Association and invited Lucretia Mott, Whittier, Emerson, James Russell Lowell and others to give talks in the community. A concern of the Friends was women's rights and Ann must have heard Lucretia Mott and other Quaker men and women discuss this question with the same fervor with which they talked against slavery.

Ann attended a boarding school in West Chester, was an eager student, studied Latin and read widely. Her letters written to young friends at this time show the normal teen-age girl, interested in sight-seeing, in the young men whom she met and in writing verses. A small volume—*Cousin Ann's Stories for Children*, dated 1849, contains highly moral stories in verse, a gentler Quaker version of *Slovenly Peter*. Other verses, one on the death of her sister, also remain to us.

After finishing her studies, Ann taught school for a few years until her mother's poor health called her home. She took over the care of the household and of her six healthy young brothers. Then it was that she began to wonder why her two younger sisters had died at an early age and why so many young girls had such poor health while the boys were strong and vigorous. When she taught her medical students later, she preached the need for exercise, sunshine and good food and freedom from all the artificial restrictions imposed on the "young ladies" of the time.

Only quotations from her Journal remain to us; the complete diary has never been found. So we cannot tell just when she began to feel the burning urge to study medicine and to use it to help women. Her friends like Lucretia Mott were pressing the cause of women's rights in an effort to get legal equality for women. Ann was interested in freeing their bodies and minds from the false modesty and old customs that kept them from developing physically and mentally.

She was thirty-seven when she began to study medicine. First she spent a year with Dr. Nathaniel E. Moseley as her preceptor. He was a brave man; despite the opposition of his fellow doctors, he had at one time five women studying with him preparing themselves to enter the Female Medical College of Pennsylvania.[3] Ann entered the College in 1850 as a member of the first class and after the required two courses of lectures received the M.D. degree as one of the eight graduates of the Class of 1852. These graduates presented theses and the handwritten copies in fine Spencerian script are in the college library. In "A disquisition on general diagnosis" Ann Preston

[1] Read before the Section on Medical History, The College of Physicians of Philadelphia, 9 February 1965.

[2] President and Dean Emerita, The Woman's Medical College of Pennsylvania, Philadelphia 19129.

[3] The name was changed to The Woman's Medical College of Pennsylvania in 1867.

Fig. 1. Ann Preston, M.D. (1813–1872). Portrait by Carol H. Beck at The Woman's Medical College of Pennsylvania.

warns against the hasty examination and the indiscriminate use of drugs which may mask the symptoms and make the patient worse instead of better. She wrote:

"Physiology has been styled 'the poetry of Medicine' but it is not merely the finishing grace; it is the strong foundation upon which the whole edifice is based": and,

"Multitudes have been depleted for visceral lesions whose primary disease was anguish of spirit. . . . Insanity and nervous diseases are directly connected with this mutual action (i.e. spirit and body) and there is not a disorder from a scratch on the toe to any inflammation of the brain that may not be modified by mental emotions."

After a year of further study, Ann Preston, M.D., was appointed in 1853 as Professor of Physiology—the first woman to hold a chair in a medical school. She worked hard to give her students the "strong foundation" which she knew physiology to be. She recognized the

importance of laboratories and of bedside teaching and knew that lectures only could not train a physician. Women were not admitted to the teaching clinics or to the hospitals of the city. They could serve as nurses on the wards, and thus Elizabeth Blackwell while a student at Geneva, and after her, graduates of the Female Medical College were admitted to Blockley as nurses. There were no trained nurses at this time so that the experience must have been difficult as well as valuable. Ann Preston determined to secure for her students the necessary hospital training.

The Civil War brought problems to the struggling medical college—a dwindling student body and a desperate need for funds. In 1861 it was decided to close the College for a year and to reorganize and strengthen it. To Ann Preston the most pressing problem was to found a hospital which women could control thus assuring women doctors and women medical students of the opportunity to treat patients.

The College had announced in 1858 that "Under the auspices of the Board of Lady Managers, a woman's hospital is to be founded in conjunction with the College, which will supply a most needed charity and offer the students of the College opportunity for both clinical and bedside training as well as give an opportunity for the training of nurses." The names of the College Corporators headed this announcement, followed by a list of the Lady Managers—Wharton, Morrison, Dreer, Stotesbury, Yarnall and other familiar Philadelphia names, showing the interest that Ann Preston had been able to arouse in the cause of women doctors.

With the help of this group, Dr. Preston spent the year in which the College sessions were suspended in raising money for the new venture. She visited old and new friends of the College to secure the necessary funds. She also planned for staffing the hospital by encouraging Dr. Emeline Horton Cleveland, a graduate of 1855, to go to Paris where she could obtain obstetrical training and also learn details of financing and administering a hospital. She was to be the first resident physician in the new hospital.

By the time that Dr. Cleveland returned, having taken five prizes for excellence and having had to learn French in order to study medicine, Dr. Preston had secured the total amount needed for the new hospital and a suitable house on North College Avenue had been leased. When the College reopened in 1862 rooms for teaching were rented in the hospital. Some of the students lived in the hospital and helped to care for the patients. Now Ann Preston had realized her dream—a college and hospital under one roof, where women were welcome.

In the charter of the Hospital, dated 1861, the purposes are clearly stated: to treat women and children; to furnish clinical instruction to women medical students; and to give practical training for nurses. From the day of opening the first two purposes were fulfilled but the training of nurses was delayed. There were no schools of nursing in the United States. In spite of Florence Nightingale, the Sairy Gamp picture of a nurse persisted and it was difficult to enlist any recruits young or old to enter a non-existent profession. Ann Preston knew the value of good nursing in the care of the sick. She wrote and talked and promoted the idea of nurses' training but it was not until nine years after the hospital opened its doors that in the Annual Report this statement is included:

"A capable and intelligent woman occupies the position of head nurse and assists in the training of the less experienced; and several promising nurses who have resided in the hospital for some months are almost or altogether ready for outside labor. Their places will be filled by fresh recruits and we trust a few accomplished nurses from this Institution will go out to bless the community from year to year." By 1871 four nurses and four medical students "are constantly in the service of the Institution."

Ann Preston had achieved her goal—a hospital where women doctors could practice, medical students be taught at the bedside, and

with the beginning of the first school of nursing in the United States, nurses could be trained. Unfortunately in later years the Woman's Hospital withdrew from its connection with the College. The recent closing of the first school of nursing and its hospital would have been a great grief to Ann Preston, but perhaps her patience and wisdom would have prevented the first separation of these sister institutions.

The founding of the Woman's Hospital was a splendid milestone of progress for the College. However the small hospital admitting only women and children did not satisfy the hopes and ambitions of the faculty for securing the best clinical training for their students. When in 1866 Dr. Preston was appointed the first woman dean of the College, she sought clinical opportunities in other hospitals. Permission was obtained for the students to attend the general clinic in the Blockley amphitheatre and their first class was made pleasant by a gracious and generous welcome from the distinguished Dr. Alfred Stillé. The next year with the permission of the Managers, Dean Preston accompanied some thirty of her students to the general surgery clinic at the Pennsylvania Hospital. To their dismay the men students welcomed them with groans, cat calls and whistles, threw paper wads and other missiles at them. This was the more surprising as attendance at Blockley had been accompanied by no unpleasant incidents. Surprising too was the action of the University of Pennsylvania and of Jefferson Medical College and of the medical staffs of various hospitals and of members of the medical profession at large who joined in writing a strong protest against the clinical instruction to mixed classes of male and female medical students, pointing out the grave impropriety of such instruction. Dean Preston and her faculty replied to this protest in a dignified and well argued statement. The Managers of the Pennsylvania Hospital refused to be intimidated by rude students and prejudiced men physicians and continued their permission for the women students to attend. In subsequent years many other hospitals opened their doors and satisfactory clinical opportunities were secured.

Dean Preston had one more battle before her. The doctors who opposed attendance at teaching clinics did not welcome the woman physician to medical practice, to medical societies or to consultations. In 1858, the Board of Censors of the Philadelphia Medical Society passed the following recommendation:

". . . the Censors respectfully report that they would recommend the members of the regular profession to withhold from the faculties and graduates of the female medical colleges all countenance and support and that they cannot, consistently with sound medical ethics, consult or hold professional medical intercourse with their professors or alumnae." A second female medical college staffed by irregular doctors had been started and this irregular institution, which closed very shortly, was made the excuse to refuse recognition to the "regular" College.

The College had a strong friend in Dr. Hiram Corson, a Quaker doctor in Montgomery County. That County Society, as well as Lancaster County, asked the State Society to recognize "the right of women as members of our profession if they recognize the code of ethics and act in accordance with its provisions." These petitions were tabled by the Society. In 1866, Dean Preston and the officers of the Board of Corporators sent a dignified and persuasive appeal to the State Society; when this was ignored they sent another. The Philadelphia County Medical Society issued a manifesto, listing various reasons why women should not be doctors and confirming their earlier position. The answer which Ann Preston published is a remarkable document, well reasoned, good tempered, logical. It begins:

"Although shrinking from all controversy and seeking the quiet path of duty the time has come when fidelity to a great cause seems to demand that I should speak for myself and for the women with whom I am associated in this movement and give a reason for the course we are pursuing."

She refuted each point of the manifesto and

ended:—" . . . on behalf of a little band of true hearted young women who are just entering the profession, and from whose pathway we would fain see annoyance and impediments removed, we must protest in the sacred name of our common humanity, against the injustice which places difficulties in our way, not because we are ignorant or pretentious or incompetent or unmindful of the code of medical or Christian ethics but because we are women."

In spite of this eloquent statement it was not until 1888, long after Ann's death, that the first woman was admitted to the Philadelphia County Medical Society. Dr. Hiram Corson and other champions working with the officers of the College and with the women doctors carried on the battle until it was won.

Ann Preston was an excellent teacher and an enthusiastic one. She taught not only in the classroom but in her Introductory and Valedictory addresses we find wise counsel, discussions of medical ethics, of problems of medical education and practice. In one address she said:

"Women must subdue opposition by showing the world that it is unjust. . . . They must earn a reputation before they can rightly enjoy its advantages; and their position, both social and professional, will depend, at last, upon what they are."

And again: "Need I say . . . that gentleness of manner and the adornment of a quiet spirit are as important to the physician as to the woman?"

"We have to live but one day at a time, to learn things one by one, and difficulties vanish and the pathway 'opens as we go along'."

So interesting were her lectures that many of them were published at the request of the audience. For some years she gave a series of lectures to the ladies of Philadelphia and of New York on "The Laws of Life and the Means of Preserving Health". In an announcement the Philadelphia Inquirer said, "Let our ladies look to this and independently of the known ability of the Lecturess the paramount importance of the subject will secure a full class". Resolutions signed by Sara Josepha Hale, E. J. Lippincott and others thanked Dr. Preston for her "forcible and perspicuous reasoning, richly imbued with true Christian faith, clothed in language chaste and pure and inculcated with a feminine delicacy not to be surpassed".

During the six years of her Deanship, this remarkable woman continued to teach both in and out of the classroom, to write, to lecture, to administer the affairs of the College, to serve actively on the Board of the Hospital and to take every opportunity to strengthen the position of women, not only in medicine but in assuming leadership of important causes. By example and precept she inspired her students and her colleagues with her courage and her strong sense of justice. Before entering upon the study of medicine she had shown her courage by helping a fugitive slave escape. Her parents worked with the Underground Railway that helped slaves to freedom. One Sunday morning, her father and mother being at Friends' Meeting, a slave was brought to the house for refuge. Shortly came the warning that the slave catchers were searching houses nearby. Ann hitched the horse to the carriage, dressed the slave in her mother's clothes with the thick double veil often worn by Quaker ladies and set out to meet the pursuers. The men saw two ladies going to Friend's meeting and Ann, unharmed, drove on to take the woman to a house which had already been searched. The fugitive reached Canada safely.

In the brief period of her Deanship, she saw gratifying progress at the College, in the curriculum and in the number of students. In 1869 she instituted a "progressive course"—that is the sciences were taught first, the students were examined and then they entered upon their clinical subjects. In the Annual Announcement for 1873 it is noted that "it is a satisfaction to find that this plan since our adoption of it has been introduced at Harvard University, Cambridge, and has met with general approval of the medical profession".

Dr. Preston's health, following an early attack of acute inflammatory rheumatism, had never been good but she never asked quarter

because of her health or because she was a woman. In 1871 a second attack left alarming symptoms. Although she resumed her work for a brief time, she died in April 1872, greatly mourned by her colleagues, her students and the whole community.

The portrait which hangs in the College is a symbol to the young women who come as applicants and students. (Fig. 1) They see that serene and lovely face and the "adornment of her quiet spirit"; they feel the power of this gentle woman who could when necessary leave the "quiet path of duty" to do battle for the rights of human beings.

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Original sources—the Annual Announcements of the Woman's Medical College and of the Woman's Hospital of Philadelphia, and personal correspondence of Dr. Preston—furnished much of the material for this paper. *The History of The Woman's Medical College of Pennsylvania, 1850–1950*, by Gulielma Fell Alsop, M.D. Philadelphia, 1950, J. B. Lippincott Company, was an invaluable source of information and of references.

Dr. Chevalier Jackson: President of The Woman's Medical College of Pennsylvania, 1935-1941[1]

By EMILY LOIS VAN LOON, M.D.[2]

IT IS entirely appropriate to talk about Dr. Chevalier Jackson in this program about The Woman's Medical College, because Dr. Jackson believed in the ability and skill of medical women and proved it by word and deed. He was associated with the College for many years and was always interested in its progress.

After his graduation from Jefferson Medical College in 1886 and postgraduate study in Europe, he began the practice of Laryngology in Pittsburgh. He became increasingly interested in the larynx and the problems of endoscopy, which at that time carried a very high mortality. The mechanical problems involved in foreign body removal challenged his ingenuity and he devoted more and more time to developing this new branch of medicine. His first assistant was Dr. Ellen Patterson, W.M.C. 1898, with whom he worked for many years. He repeatedly stated that a woman's sensitive fingers were particularly adapted to the delicate nature of endoscopic manipulation. When he left Pittsburgh to return to Jefferson as Professor of Laryngology, Dr. Patterson then became chief of the Endoscopic Clinic in Pittsburgh.

In 1925 he was appointed Special Lecturer on Bronchoscopy at The Woman's Medical College and every year at the request of Dr. Margaret Butler he talked at least once to her Laryngology class. His lectures were always dramatic for he once said that in teaching medical students the primary requisite was to keep them awake. He illustrated his talks by his famous chalk drawings done bimanually with colored chalk. In his lecture on tracheotomy, he sketched a patient almost dead of asphyxia and then by a few strokes changed the picture to a smiling, grateful patient who was saying "thank you".

Dr. Jackson's whole life was dedicated to the perfection and expansion of Bronchoesophagology and to the dissemination of this knowledge all over the world. To this end he established a Clinic at Jefferson and when it was functioning smoothly, opened one at the University of Pennsylvania, then another at the Graduate Hospital. Next came one at Temple University Hospital. During this period, he was giving intensive courses and lectures to physicians, who came from all over the world, and he himself travelled to Paris repeatedly to give courses there. In 1934, while he was at Temple, he decided that there should be a regular organized Bronchoscopic Clinic at The Woman's Medical College where we had been doing only an occasional case.

With typical determination and tact, he presented the idea to the Board of the College who created the chair of Bronchoscopy and Esophagoscopy with Dr. Jackson as Professor. We acquired the necessary equipment and began our weekly Clinics, talking about our endoscopic work to anyone who would listen so that the Staff would realize that the Bronchoscopic Clinic was functioning. Occasionally, to encourage us, Dr. Jackson sent in a private patient of his own. This entailed considerable inconvenience as he would have to dress, scrub, do the case and then change and go to Temple where the rest of his cases were waiting, and where his battery of assistants, nurses and secretaries were organized

[1] Read before the Section on Medical History, The College of Physicians of Philadelphia, 9 February 1965.

[2] Professor Emerita of Otolaryngology and Bronchoesophagology, The Woman's Medical College of Pennsylvania, Philadelphia 19129.

to make things move smoothly. But every Wednesday morning, private patient or no private patient, Dr. Jackson would come to the college, meet me in the foyer and say, "Good Morning Doctor, is there anything for me this morning"? I would reply, "No Dr. Jackson, not this morning". Whereupon, he would make a deep bow and say, "Thank you very much", and then go the Dean's office where he would leave a ceremonial calling card.

Twice, he gave the commencement address at the Woman's Medical College. It was not an oration he said, just advice on their future in medicine, gathered from his forty years of experience. He ended both talks by saying, "If in any of the four corners of the earth to which you will scatter, you need someone to vouch for you, write to me and after your signature, put Woman's Medical College." This was not just idle talk: a few years later one of the class had been unsuccessful in getting an appointment to a nose and throat residency in a New York hospital which had never admitted women. She timidly presented her problem to Dr. Jackson, who immediately telephoned to the Chief of Service of the hospital and the appointment came through promptly.

In 1935, at seventy years of age, Dr. Jackson further indicated his interest in the College by accepting the Presidency of the institution. He served until 1941, adding the responsibility of that office to his already heavy schedule. He was instrumental in furthering the development of the institution during those years. In one of his speeches while President he commented on the value of medical education for a woman, "whether she continues to practice or not, no education could better fit a woman for raising a family, and it is absurd to regard the medical education of a woman as a total loss if she does not practice." He also said: "I hope that I contributed a little to bring about the breaking down of the old prejudice against the woman physician". It was at this time that he made an etching of the College building and had it reproduced as his Christmas card. It was his custom to do an original painting or etching which was then reproduced and mailed to friends and associates all over the world at Christmas.

Dr. Jackson's strong sense of theater showed in the conduct of his Clinic. Nothing was ever casual and nothing was allowed to divert attention from the main issue, which was the patient. A sign over the scrub basins, "No talking except in the interest of scheduled patients", meant exactly that. The patient was brought into the darkened operating room only when everything was ready, the tubes lit, the staff waiting. A sign "Silence" was turned on and only directions to the patient broke that silence. Request for instruments were made by hand signals and seldom was a word needed. This restraint was carried out also in examining and conference rooms. No words were wasted. A patient who had been sent from California would ask questions about what had been found at his examination, what was the prognosis, what should be done. He would be stunned to hear Dr. Jackson say, "The examination was satisfactory, you may go home tomorrow. Your doctor will receive a full report and will carry out your treatment." Period.

He was always meticulous, and prepared for any emergency which could possibly be anticipated. Each endoscopic light was tested with each cord before using, each forcep and dilator checked through the tube before the case began. One felt that as the pioneer of endoscopy, he saw not only the fate of the patient but also the reputation of his speciality involved in every case. Its motto, "Educate the eyes and fingers", applied in the highest degree to his own practice. He would try forceps on a duplicate of the foreign body before attempting its actual removal. If the forceps available did not appear adequate, he would devise new ones to meet the problem. In a special place in the Clinic was kept a string of safety pins of ascending sizes which could be checked against the x-ray films for size in selecting tubes and forceps. This string was always referred to as the 'Bronchoscopic Rosary'.

Dr. Jackson campaigned tirelessly in his efforts to eliminate conditions which are harmful to the well-being of children. He treated thousands of children who had inhaled or ingested foreign bodies and he was appalled by the carelessness and ignorance which permitted these accidents to occur. He spent much time and effort in an educational campaign to the medical profession, to nurses, and to the laity, aimed at spreading information about foreign body prophylaxis. His pamphlet, "What does your baby put in his mouth?", was a classic warning to mothers. It contained x-ray pictures of open safety-pins, toys, coins, etc., in chests of children and carried pithy warnings such as, "Peanut candy is often fatal to babies", "Safety pins have killed more babies than have firearms", "Small toys are fraught with danger to small boys". This pamphlet also contained a list of twenty important factors in foreign body prophylaxis. One suggestion was that food or bones lodged in the esophagus were due to "hasty gluttonous eating". Probably his most difficult foreign body was in a nine-months old baby whose older sister had fed him four open safety pins entwined with strands of wool. These were successfully removed.

Another arduous campaign against an evil which threatened the lives of children lasted for twenty-five years. The frequency and the frightful results of ingestion of lye by children started his long effort to get the poison label on the lye can. The manufacturers refused to do this voluntarily. Dr. Jackson, as Chairman of the Committee on Lye Legislation of the Laryngology Section of the A.M.A., enlisted members from every state in the Union. They besieged the state legislatures and after twenty years, pertinent laws were enacted in twenty-four states. Finally, as the Federal Government showed increased interest in the regulation on interstate commerce, it appeared to be advisable to seek Federal jurisdiction. After many trips to Washington and hours spent in interviews with committees, the Federal Caustic Act, providing for a poison label and a description of the antidote, was passed and signed by President Coolidge on March 2, 1927.

Dr. Jackson's honors and awards from all over the world are too numerous to mention: they cover two full pages in his autobiography. He always wore the ribbon of an Officer in the French Legion of Honor in his buttonhole, and his office walls were almost covered with citations. To those who worked closely with him, I believe, we remember best his absolute dedication to the field of Endoscopy and the benefits it offered to patients and his missionary zeal in diffusing this knowledge throughout the world. We remember his formal courtesy to all his associates and to his patients. We will always remember his iron determination to push to completion the work which he thoroughly believed in.

Memoir of Bernard Mann (1883-1964)*

By LEWIS C. SCHEFFEY, M.D., SC.D. (HON.), L.H.D. (HON.)

THE activities and accomplishments of Bernard Mann were many. Born in Austria on February 12, 1883, he graduated from the University of Pennsylvania School of Medicine in 1909. Early in his career the specialty of obstetrics and gynecology absorbed his interest and he soon attracted the attention of Dr. Barton Cooke Hirst, then professor of obstetrics at the University of Pennsylvania. Dr. Mann interned and was trained in his specialty at the Howard Hospital under Dr. Hirst's tutelage, first as a gynecologic pathologist and later in the clinical and surgical disciplines. He remained at that institution until about 1927 when he was appointed Chief of Gynecology Service II at the Albert Einstein Medical Center, Southern Division, then known as Mt. Sinai Hospital. From 1942 to 1947 he was its Medical Director. He was chairman of the Medical Board for fifteen years until retirement. When in 1931 the now extinct Northern Liberties Hospital sought a Medical Director, he was called and accepted. He was also a consultant at the Eagleville Sanitorium. From 1926–36 he served as Associate Professor of Gynecology at the University of Pennsylvania Graduate School of Medicine. In all of these posts he worked hard, fulfilling broad responsibilities.

He was a member of the American Medical Association, Pennsylvania State, and Philadelphia County Medical Societies. He was a Diplomate of the American Board of Obstetrics and Gynecology, Fellow of the American College of Surgeons, and a Fellow of the College of Physicians of Philadelphia. In 1946 he was elected President of the Obstetrical Society of Philadelphia and served well his term of office.

There were two passions in Dr. Mann's life. One was his pride in and devotion to his family and the other, his attachment and loyalty to the Albert Einstein Medical Center. During his tenure as Medical Director he was frequently approached to consider the applications of various individuals for advancement or for staff position. He would give his wholehearted support if he felt that the applicant met his criterion of loyalty to the institution. He continued an active interest even after retirement; his last visit was made on the day before he died.

Dr. Mann was a sensitive person. He loved flowers, paintings, and beautiful objects of art. He was an esthete and collector. His collection of postage stamps was a comprehensive one. He gathered a complete collection of Presidential signatures, from George Washington to Franklin D. Roosevelt. He was proud of his fine collection of etchings, including an original by Rembrandt.

Dr. Mann died on August 3, 1964. He is missed by many former patients and colleagues and missed most by those who knew him best.

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A Treatment of Burns[1]

By CARL A. MOYER, M.D.[2]

NONSYMPTOMATIC or objective treatment of any biologic disorder rests upon the physician's ability to remove the cause of the disorder, to lighten environmental loads having either a positive or a negative quality, or to substitute physically, chemically or mechanically for deficient organ functions.

In the case of burn therapy, removal of cause of the injury, thermal energy, is now recognized to be impossible. However, as long as heat was held to be a substance called "caloric," and was thought to continue its deleterious action in the burned part until it was dissipated into the air or was removed by caloric absorbers such as cold water and ice—icing or otherwise cooling a burn was considered to be proper scientific treatment. Icing burns is still practiced, although the scientific reason for its being done in the first place has been proven false.

Today, there are only two avenues open for the development of the objective treatment of burns: one, to lighten biologic loads imposed by the injury, and the other, to substitute for deficient organ function. The first requires a fairly detailed knowledge of the alterations in the physical-chemical characteristics of the macromolecular protein complexes making up skin that take place when the skin is subjected to high temperatures. Some of the questions that can be asked about skin being burned are: What are the changes in the adsorption coefficients of collagen for water, sodium, potassium, etc.? What changes occur in the structure and positioning of the cutaneous lipids that play such a critical role in the genesis of skin's impenetrability to water and ions? What are the effects of desiccation, over-hydration, and bacterial growth upon the macromolecular structure of collagen, etc.? Today, there is no answer to any of these questions!

One thing is known: burned skin and tissues beneath it are soon swelled with a fluid predominantly containing sodium salts and a little blood-protein (4). This occurs presumably because the blood capillaries in the region of the injury are leaky. A superficially logical, but not an objective, theory because normal capillaries are freely permeable to ions and water. We have further presumed, without correlative measurement, that shock attendant upon large burns is related practically in entirety to the impoverishment of the blood of plasma by the swelling of the burned parts,

[1] Nathan Lewis Hatfield Lecture II, The College of Physicians of Philadelphia, 6 January 1965.

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and have staked our faith on plasma transfusions to treat burn-shock.

To be sure, there is some evidence that some blood vessels somewhere in the region of the burn are leaky; radioactive plasma proteins put into the general circulation collect in the area of injury (5). But, this is not the whole story! The hurt tissues contain large amounts of fibrous macromolecules having large surfaces upon and in which water and hydrated ions are normally adsorbed and incorporated into the fibrous molecular structure. Could not the heating of these molecules increase their adsorptions of water and ions and result in swelling of the organ without the blood vessels becoming leaky? Sterile scalded skin taken off a rat's tail immediately after the injury, weighed, and then inserted aseptically into a subcutaneous tunnel beneath uninjured abdominal skin of the rat from which the tail skin was removed, gains as much as 45 per cent of its original weight in four hours—*while it has not been connected to a single blood vessel* (2) Fig. 1.

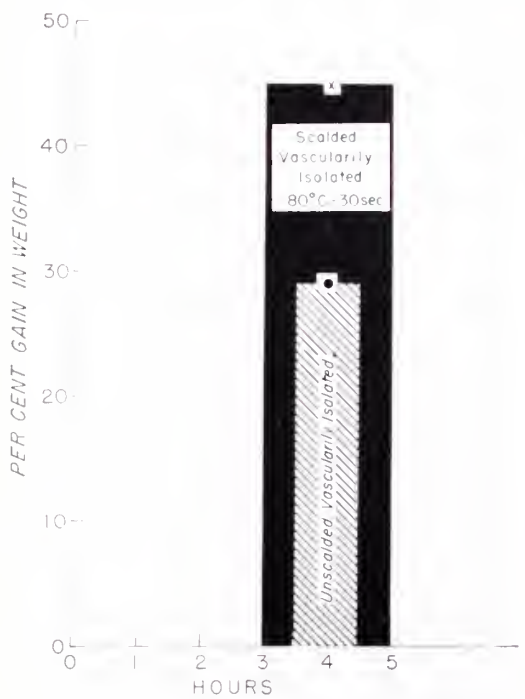

FIG. 1. Gain in weight, per cent of original, of avascular rats' skins, burned and unburned, removed aseptically from the tail and inserted aseptically beneath the skin of the abdomen of the rat from whose tail it was taken.

Unscalded skin of a rat's tail, treated in the same fashion, gains about 25 per cent of its original weight in four hours, while it, too, has been completely disconnected from the vascular system. These simple experiments demonstrate without a doubt that physical-chemical alterations taking place within vascularly-deprived, and the vascularly-isolated, thermally-injured skins that effect their taking up large quantities of salts and water are factors that could be a major cause of burn-swelling and of burn-shock. They even indicate that some of the burn-swelling might well be due to partial vascular isolation of tissue within and beneath the burned skin rather than to increased vascular permeability. These observations serve to point up the need for the genesis of biologic concepts of illness attending injury that take into account more than the workings, structure and integrity of the vascular system, and the workings of the endocrine and nervous systems.

Investigators and physicians believing that increased capillary permeability was the cause of burn-swelling, and that increased tissue pressure should limit it, have attempted to prevent and treat burn-shock by limiting the swelling of the burned part with the application of pressure. Only rigid encircling casts about burned extremities have done this, but—at the cost of ischemic gangrene of the distal members such as toes, foot and leg. Should increased adsorption of water and salt by thermally-injured macromolecules rather than increased capillary permeability be the cause of burn-swelling, mechanical pressure could not limit the swelling without inordinate compression of the uninjured tissue beneath the skin, because adsorption pressures are often very large, being as high as 37,000 atmospheres in such simple systems as water and charcoal (13).[3] However, should altered adsorption of water and ions by macromolecules be the cause

[3] One milliliter of water in 10 grams of gas-free charcoal.

of burn-swelling, the development of safe chemical means of reversing it should be possible, and the treatment of burn-shock could be made extraordinarily easy. However, this removal-of-cause approach to the treatment of burn-swelling and shock is only a dream, and, until it is realized, the only approach to treating burn-shock is to lighten the internal-environmental loads imposed by the swelling. To do this, the biologically-important negative loads must be identified by experiment and not by logic.

Identified internal-environmental loads imposed upon the uninjured parts by a large burn are: a negative vaporizational heat load (3), oligocythemia (reduction in circulating red blood cell mass) coupled with polycythemia (elevated hematocrit), a deficit in total circulating blood proteins, a negative load of sodium salts and water and a positive extracellular load of potassium ions. Which of these are biologically important and what are their relative importances? The negative load of circulating plasma protein has been taken to be it, basing choice upon the assumption that Starling's hypothesis is the law of blood volume, and that burn-shock is oligemic in origin.

However, let us examine certain correlations that can be made during the treatment of burn-shock with a non-colloid containing saline solution alone, and then draw what conclusions we may.

During three years, the treatment of burn-shock in the Hartford Burn Unit of Saint Louis[4] has been conducted—with but one exception—only with lactated-Ringer's solution (pH adjusted to 8.2) to meet the sodium deficit in uninjured tissue caused by the swelling of the burn-wound, while the negative vaporizational heat loading through the wounds has been controlled by one of the three means, namely: 1) continuous immersion in a bath of Locke's solution (T. 36°C. ± 0.5°); 2) restitution of the water barrier to the epidermally-denuded dermis by impregnating it with oleic acid, and thereby stopping the transdermal capillary water flux (10), and; 3) the continuous coverage of the wounds with a thermo-pack wet dressing containing a 0.5% aqueous solution of silver nitrate as a bacteriostatic agent. These steps, to minimize the negative thermal load, were taken in order to remove a complicating environmental variable.

This examination of the efficacy of a saline solution in the treatment of burn-shock is restricted to those cases *in which shock existed or was certain to occur*, should no treatment be given. Consequently (excepting one deep burn covering 30 per cent of the body of a young man (W. G.) who was blown in flames off a 10-foot platform onto a concrete floor, and who entered the Burn Unit in shock and anuric), only cases of deep burns[5] covering 40 per cent or more of the body surface, and wholly treated in the Hartford Burn Unit, are included in this series.

No glucose solution, no plasma, no dextran, no blood (except for 500 ml. in the case of D. W.), no solute diuretic, and no water was given during the treatment of shock. No pooled or stored plasma, no dextran, and no solute diuretic was given to anyone at any time during convalescence. There was not a death from shock. There was not a case of renal insufficiency, although in two cases the hemoglobin concentration in the first 50 ml. of urine excreted after starting treatment exceeded 500 mg. per cent. Pulmonary edema did not occur, although gains in body weight during 48 hours varied between 10 and 42 per cent (see Table I).

Not one tracheostomy was performed or needed, because there were no serious respiratory difficulties, in spite of the fact that burns covered the faces and necks of 7 of the 10 individuals.

Venous pressures were measured hourly during the intravenous infusion of the lactated-Ringer's solution. Only in the case of L. S. (85 per cent full-thickness burn) did it

[4] Hartford Burn Unit since July 1, 1963.

[5] Burn areas that healed in 21 days *were not counted*. Such burns are only shallow injuries and are not biologically very important.

TABLE I

PER CENT GAIN IN BODY WEIGHT DURING THE FIRST 48 POST BURN HOURS AFTER TREATING BURN SHOCK WITH LACTATED RINGER'S SOLUTION

Patient	Age	Treatment of Wound	Deep Burn* % B.S.	Per Cent Weight Gain	Final Outcome
D. W.	25 years	$AgNO_3$	70%	18%	Survived
W. G.	24 years	Oleic Acid	30%	8.3%	Survived
L. T.	64 years	Oleic Acid	40%	18%	Died of sepsis on the 13th day (Pseudomonas py.).
S. H.	10 years	$AgNO_3$	65%	24%	Survived
W. H. *See case* W. H.	4 days	$AgNO_3$	60%	42%	Died on 12th day of negative thermal load and bronchopneumonia.
L. Bo.	6 years	Locke's Bath	65%	11.5%	Died of sepsis on the 22nd post burn day (Pseudomonas py.).
D. S.	57 years	Oleic Acid	80%	12%	Died of hypothermia and sepsis on the 4th post-burn day.
C. St.	24 years	$AgNO_3$	75%	Data not obtained	Died of potassium deficit on 41st day.
L. S.	18 years	$AgNO_3$	85%	26%	Survived
D. H.	18 years	$AgNO_3$	40%	10%	Survived

* Minor injuries constituted of epidermal and superficial dermal burns that healed within 21 days after the burn are excluded from these estimates.

rise above normal and then for only an hour. Upon slowing the rate of the infusion, it quickly returned to normal.

The correlation of the changes in hematocrits in these cases with rates of flow of urine (Table II) and signs of shock such as, apathy, disorientation, nausea, vomiting, tachycardia and weakness, demonstrated that recovery from anuria, disorientation, nausea, vomiting and weakness *occurred while the hematocrits rose* significantly in 6 cases out of 10. Assuming that red cells were not being added to the circulation in significant numbers from bone marrow and other places, an assumption that is warranted because all studies of burned animals (Lesser's being the first) show the opposite, one may conclude that *recovery from burn-shock was effected by the infusion of Hartmann's solution in 6 of 10 cases while hematocrits were rising and oligemia was increasing.* In this series of cases, the percentile changes in blood volume, calculated from changes in hematocrits that occurred while recovery from burn-shock was effected with lactated-Ringer's solution, are tabulated in Table III. Only in two cases—one, a child four days old (W. H.), and the other, a child of six years (L. Bo.)—did the hematocrit and oligemia decrease significantly during recovery from burn-shock; in two cases (L. T. and D. S.), the hematocrit did not change, and in the other six cases, it increased significantly, indicating that decreases in blood volume of from 7 to 20 per cent took place while all signs of shock disappeared.

The lack of correlation between the physical incapacity manifest by the burned individuals treated with Hartmann's solution and the high hematocrits indicative of increasing oligemia is illustrated in Figure 2, A and B. Photo A was taken 18 hours and 30 minutes after the infusion of the saline solution was begun; 8,825 ml. had been given intravenously during 14 hours when the intravenous catheter was removed and full dependence placed upon the drinking of a hypotonic saline solution. He had drunk 1,400 ml. of this before the photo was taken. He had eaten a good breakfast at

TABLE II

URINARY SECRETION (ML./HR.) IN RELATION TO PERIPHERAL HEMATOCRIT DURING AND AFTER TREATMENT OF BURN SHOCK WITH LACTATED RINGER'S SOLUTION WITHOUT PLASMA OR DEXTRAN (DEATHS FROM SHOCK—NONE)

Case	Hours After Beginning Treatment																						Deep Burn* % B.S.	Wound Treatment
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60			
D. H. UV/h	+	35		22	25	50					34		55		45								40	$AgNO_3$ wet
Hct	50	58			58		60	62		60						52		41						dressing
W. G. UV/h	47		35	95	136	88	113	85	120	73	105	150											30	Oleic acid
Hct	49	55	57			50		51							53									
L. T. UV/h	+			37		34			33				28		23		36		36				40	Oleic acid
Hct	61	67				60									53			53						
S. H. UV/h	○					58		68	85	70	51	43	40	40	38								65	$AgNO_3$ wet
Hct	54					60			64						55				52					dressing
W. H. UV/h	○	10		22		15		27		23			32										60	$AgNO_3$ wet
Hct	65	64	61		50	45				41			40			40			35		35			dressing
L. B. UV/h	+	18			24	25				16				21		55		44		44			60	Locke's bath
Hct	48				53	45								38	39				39		34			
D. S. UV/h	○	66	53	35	15	30		14	44	22	10	24	30	20									80	Oleic acid
Hct	65	64	62					62										62						
C. S. UV/h	○		53			94				23				45	52			31		50			75	$AgNO_3$ wet
Hct	50	53		56						62								63						dressing
L. S. UV/h	○	41	21	27	26	43		35	40	46	50	62		73	78	82	90	71					85	$AgNO_3$ wet
Hct	58	56	55	58	62	65					62		60	60				51						dressing
D. W. UV/h	○		45		34				35				59		61		60		54		59		70	$AgNO_3$ wet
Hct	51		58		61								66		64					57				dressing

UV/h—urine flow, ml. per hour, Hct—Peripheral hematocrit. +—very slow urinary excretion before treatment, ○—anuria before treatment.

All cases were adults except W. H. (4 days old), L. B. (6 years old), and S. H. (10 years old).

* Minor injuries constituted of burns that healed in 21 days are excluded from the area estimates.

TABLE III

PERCENTILE CHANGES IN BLOOD VOLUME DURING TREATMENT OF BURN SHOCK WITH RINGER'S-LACTATE; CALCULATED FROM HEMATOCRITS

Case and Age	Size of Deep Burn % B.S.	H_1 Hematocrit at Beginning Treatment %	H_2 Maximum Hct. During Treatment at Time Urine Flow was 25 ml. an Hour or More and Signs of Shock were Absent %	Change in Blood Volume in % of Volume at Start Saline Infusions $\frac{H_2 - H_1}{H_2} \times 100 =$ % Change B.V.
D. H./25	40	50	62	19% decrease
W. G./24	30	49	57	14% decrease
L. T./64	40	61	60	no change
S. H./10	65	54	64	15% decrease
W. H./4 days	60	65	45	44% increase
L. Bo./6	60	48	45	7% increase
D. S./57	80	65	64	no change
C. S./24	75	50	63	20% decrease
L. S./18	85	58	65	10% decrease
D. W./25*	70	58	66	12% decrease

* H_1 taken as 58 one hour after the transfusion of 500 ml. of blood; consequently, the calculated change in blood volume in this case applies to the time interval between the 6th and 36th post-burn hours.

FIG. 2. Case D. H. The photo A, upper right, was taken 18 hours and 30 minutes after the treatment of shock was begun. Photo B, left, was taken 20 hours after Photo A.

8:30 A.M., when the hematocrit was 58 (it was 49 when treatment was begun). He ate most of a regular diet lunch at 1:00 P.M., when the hematocrit was 60. The photo A was taken at 2:00 P.M., when the hematocrit was 62. He sat up unaided and was not faint or dizzy.

Between photos A and B, 20 hours elapsed without nausea or vomiting. He ate a regular diet and drank 2,000 ml. of saline solution containing 4 grams NaCl and 1.5 grams of $NaHCO_3$ per liter. The hematocrit was now 52 (the original was 49, when he was anuric and too weak to sit), but he could now, with an hematocrit of 52, stand and walk unaided without feeling the least faint. The deep burn-wounds he bore are shown in Figure 3. Clearly, at this time the blood volume was no greater than it was when treatment was begun 34 hours earlier, when he was anuric, too weak to sit, apathetic, and with a pulse rate of 136.

These observations and correlations prove that oligemia is not the sole cause of burn-shock, and, indeed, indicate that it may be only a minor causative factor, the more especially with burns smaller than 50 per cent of body surface, because fair restoration of physical capacity, sense of well-being, renal function, and vascular sufficiency were attainable in severely-burned human beings by providing only extracellular salts and water in amounts that, in most instances, did not effect appreciable reductions in hematocrits.

They further indicate that much of the physiological derangement making up burn-shock is related to direct cellular effects of sodium deficit in unburned tissues and not to a reduction of minute volume flow of blood

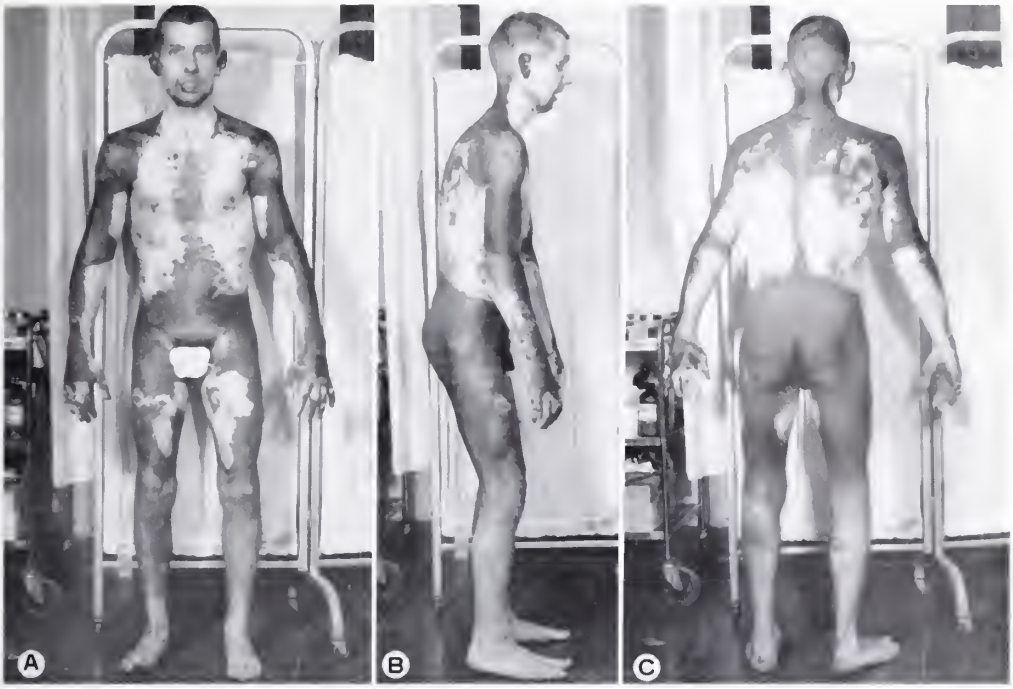

FIG. 3. Case D. H. Gasoline explosion and clothing burn 13 days old showing the deep injury. The minor injury (epidermal burns) of the face, the extensor surfaces of the hands and forearms and upper scapular regions are practically healed. No appreciable amount of healing took place between the 13th and 21st days; consequently, there was little superficial dermal burn. The unstained parts of the body, excepting the hands and face, are deeply burned and the eschar has been removed everywhere from them excepting from the small areas of the lower right back and antero-medial surfaces of both thighs. 0.5% silver-nitrated wet dressings were used continuously.

secondary to oligemia. For, if this was not true, how could one account for such happenings, as in the case of L. S.? He was in profound shock with a hematocrit of 58, and after 20,900 ml. of Hartmann's solution had been given intravenously during 30 hours, the hematocrit was 60. However, when the hematocrit was 60, there were no clinical signs of shock and the cardiac output was a normal 4.84 liters per min. with a C. I. of 2.66 $L \cdot min.^{-1} \cdot M^{-2}$. If oligemia was the cause of the shock manifested with a hematocrit of 58, he should have been no better 30 hours later when the hematocrit was 60 and the oligemia no less. This is not surprising—cardiac output and minute volume flow of blood do not decrease significantly in recumbent man until total blood volume has been reduced $\frac{1}{3}$ or the venous blood volume has been reduced 50 per cent. In this case even, should 20 per cent of the red cells be sequestered or destroyed during the burning while his normal hematocrit was 45%, the oligemia represented by the hematocrit of 58 would just be attaining a level that might produce peripheral circulatory insufficiency. The variable in the case is not oligemia; it is the mass of sodium salts and water in the *extravascular compartment*. The oligemia was unaltered by the addition of sodium to the body, but shock disappeared. Therefore, the shock must have been related to extravascular sodium deficit in unburned tissues and not to the oligemic intravascular sodium deficit which was not altered by the treatment.

We may now attempt to answer the question: What internal-environmental loads are biologically important in the genesis of burn-

shock? Isoosmolar sodium deficit is. Oligocythemia and polycythemia are not. Potassium excess is not.[6] Plasma protein deficit is not important *when the injury does not cover more than 85 per cent of the body's surface.* The answers could be much different with deep burns covering more than 85 per cent of man's body, because the treatment of such injuries with lactated-Ringer's solution only has not been observed yet.

Another question now presents itself: How does the administration of sodium salts relieve the burned person of most of the signs of shock while it often increases blood volume but little or not at all? This question cannot be answered, because we know practically nothing about the cellular effects of sodium and water deficits. About all that is known is that muscle will not long work, nerve will not long conduct, and certain isolated mammalian tissues use oxygen more slowly upon being immersed in sodium deficient media (12) (7). Questions that need answers are such as these: What are the relationships of vascular resistance, cardiac strength, renal function, hepatic function, carbohydrate, fat, and protein catabolism and anabolism and enzyme functions to the numbers of hydrated sodium ions and water molecules in the immediate environments of cell surfaces? Until there are answers to such questions, all that can be said is: isoosmolar sodium deficit in tissues other than blood is an important factor in the genesis of burn-shock for unknown reasons.

The volume of lactated-Ringer's solution required to treat burn-shock successfully in any particular case cannot be estimated; the variance of the amount needed is too great. The weight of lactated-Ringer's solution retained during the treatment of shock, relative to per cent burn, varies between 0.15 and 0.70 of one per cent of body weight per one per cent body surface covered by a deep burn. This, in seven cases out of 10, exceeded the amounts formerly recommended as safe maxima by 30 to 200 per cent, and in one case (that of an infant), by 400 per cent. (Table IV.)

The only therapeutic rule that might be proposed is: during 24 to 36 post-burn hours, give lactated-Ringer's solution fast enough to keep the burned person safely and comfortably alive, making urine, and oriented, but not so fast as to raise central venous pressure significantly and sustainedly above normal.

With a large, deep burn, treatment is only begun with the successful treatment of shock. To this day, recovery from deep burns covering 65 per cent of the body is rare, although recovery from shock can be effected regularly in such cases. Death from infection and inanition regularly ends the picture. What is the cause of burn-inanition? "Stress" is the answer usually given, which says nothing, but only stills the desire to know! The skin is the organ destroyed, so it is logical to presume that the destruction of some cutaneous function is somehow the cause. It is rather illogical to assume that impulses arising in dead, neurally-deficient skin could stimulate the holy physiologic axis of pituitary, thyroid and adrenal into increasing catabolic rate 100 per cent and more.

Dermis devoid of epidermis, epidermis devoid of stratum corneum, and stratum corneum devoid of lipids, when exposed to dry, still air, constitute surfaces from which water evaporates faster than it does from a plane water surface open to still air. This extraordinarily rapid evaporation of water from these abnormal cutaneous surfaces takes place without their surfaces being visibly wet; Table V.

All exposed and dry-dressed burn-wounds leak water evaporatively at rates 15 to 70 times faster than normal skin does, the smaller accelerations occurring when the wound is exposed to still, moist air, and the larger, when the wounds are exposed to currents of dry air. As long as the temperature of the wound surface is higher than the air or dressing covering it, the heat necessary to maintain the normal mean velocity of water molecules in the body, after the evaporative

[6] Serum K concentrations regularly remained above normal for 36 to 60 hours and the Ringer's lactate contained 5 mEq. K^+ per liter.

TABLE IV

COLLOID AND ELECTROLYTE REQUIREMENTS CALCULATED USING THE EVANS AND BROOKE FORMULAE COMPARED TO THE QUANTITIES USED IN THE HARTFORD BURN UNIT FOR THE TREATMENT OF SHOCK ASSOCIATED WITH DEEP BURNS

Pt.	Age	Wt. (Kg)	% B.S. Burn*		1st 24 Hours			2nd 24 Hours		
					Evans	Brooke	Hartford	Evans	Brooke	Hartford
	years									
L. S.	18	69	85	Colloid	3450	1725	0	1725	862	0
				Electro-lyte	3450	5175	18,000	1725	2588	2410† + 1195 P.O.‡
					6900	6900	18,000	3450	3450	3605
S. H.	10	43.6	65	Colloid	2180	1090	0	1090	545	0
				Electro-lyte	2180	3270	5400 + 1300 P.O.	1090	1635	1320 + 1120 P.O.
					4360	4360	6700	2180	2180	2440
W. G.	24	70	30	Colloid	2100	1050	0	1050	525	0
					2100	3150	11,050 + 2120 P.O.	1050	1575	675 + 5660 P.O.
					4200	4200	13,170	2100	2100	6335
D. W.	25	99	70	Colloid	4950	2475	500 Blood	2475	1238	0
				Electro-lyte	4950	7425	9400 + 1000 P.O.	2475	3712	4150 + 860 P.O.
					9900	9900	10,900	4950	4950	5010
W. H.	4 da	4.3	60	Colloid	215	105	0	108	54	0
				Electro-lyte	215	325	2675 + 188 P.O.	108	162	80 + 302 P.O.
					430	430	2863	216	216	382
C. S.	24	57	75	Colloid	2850	1425	0	1425	712	0
				Electro-lyte	2850	4275	10,500 + 2690 P.O.	1425	2138	3900 + 1290 P.O.
					5700	5700	13,190	2850	2850	5190
L. T.	64	59	40	Colloid	2360	1180	0	1180	590	0
				Electro-lyte	2360	3540	9000	1180	1770	3000 + 1065 P.O.
					4720	4720	9000	2360	2360	4065
D. S.	57	88	80	Colloid	4400	2200	0	2200	1100	0
				Electro-lyte	4400	6600	13,000 + 345 P.O.	2200	3300	4500 + 185 P.O.
					8800	8800	13,345	4400	4400	4685
L. B.	6	20	65	Colloid	1000	500	0	500	250	500 Blood
				Electro-lyte	1000	1500	1580 + 1720 P.O.	500	750	1000 + 2520 P.O.
					2000	2000	3300	1000	1000	4020
D. H.	18	75	40	Colloid	3000	1500	0	1500	750	0
				Electro-lyte	3000	4500	8825 + 1950 P.O.	1500	2250	1550 P.O.
					6000	6000	10,770	3000	3000	1550

* Minor injuries constituted of epidermal and superficial dermal burn areas that healed within 21 days after the burn are excluded from these estimates.

† Mls. lactated Ringer's with pH adjusted to 8.2.

‡ P.O. = Mls. of an aqueous solution containing 4 G. NaCl and 1 to 1.5 G $NaHCO_3$ per liter.

TABLE V

TRANSCUTANEOUS EVAPORATIVE FLUX OF WATER
Mls.·M^{-2}·hour^{-1}

Preparation	In Vitro T. = 26°C.	In Vivo T. = 32 – 34°C.
Human Skin Devoid of Epidermis	180	341
Human Skin Devoid of Lipid . .	229	
Normal Human Skin	1.57	4.3
Dry Eschar of Deep Burn		312 (6th day) 212 (11th day)

Rate of flow of dry air over skin was 2.1·20 cm.$^{-2}$·min.$^{-1}$

escape from it of those having velocities of the highest, order must be generated from exothermic chemical reactions in the body. Hence, under these conditions, the more water evaporatively lost through or on the skin, the more rapid the consumptions of oxygen and foodstuffs must be.

The hypercatabolism associated with a burn in mammals is directly proportional to the increase in rate of transcutaneous evaporative loss of water from the body. Figure 4.

Consequently, if proper means could be found to stay this evaporative loss of water from the body through burned skin and granu-

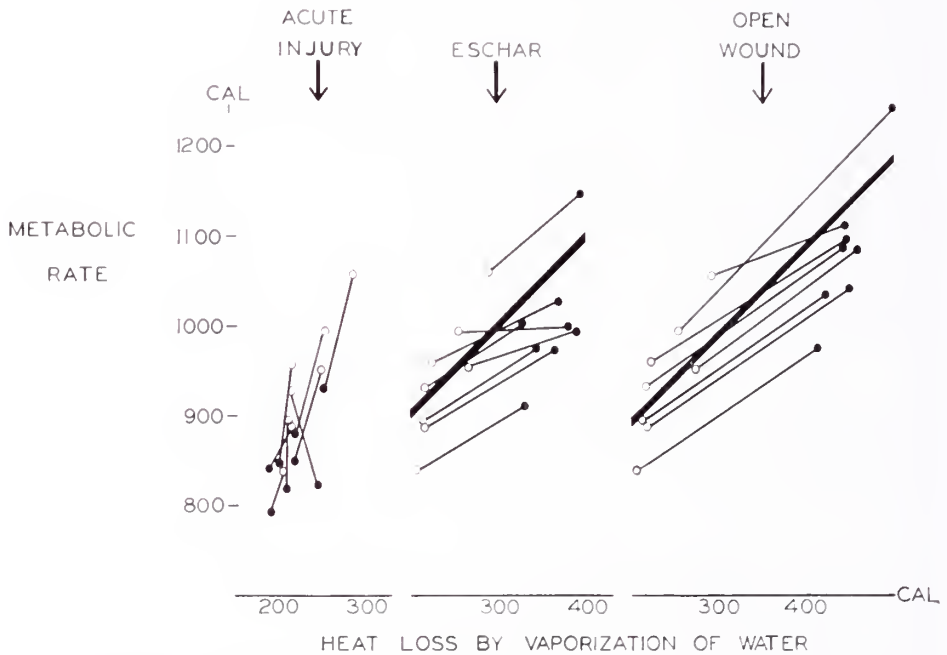

FIG. 4. The metabolic responses of eight mature white rats to full-thickness burns of their backs, covering 10 per cent of body surface. The metabolic rates were calculated from oxygen consumptions and the vaporizational heat losses from the gravimetrically—ascertained rates of the insensible losses of water, while the animals were in dry air at 26°C. The metabolic rate and heat loss by vaporization is expressed as kilocalories·M^{-2}·(24 hours)$^{-1}$. The heavy line is drawn at an angle of 45° with the Y axis. This is the slope corresponding to a 1:1 ratio of increment of total metabolic rate to increment of vaporizational heat loss. The open circles mark the positions of the metabolic rates relative to vaporizational heat losses of individual animals before the injury. The closed circles connected with the open ones mark the positions of metabolic rates of respective animals at various times after the burn: acute injury (during first 8 post-burn hours), eschar (10th to 14th post-burn days), open wound (16th to 26th post-burn days). During the acute phase, vaporizational heat loss increases relative to total metabolic rate, although the latter decreases. During the escharotic and open-wound phases, metabolic rates increase slightly less than vaporizational heat losses do, but the relationship of one to the other is close to 1:1.

lating burn-wounds, inanition should be much more readily prevented. The other therapeutic approach to the problem is what might be called the "stoker approach"—the pumping in of food of all sorts through an indwelling gastric tube. This has been beset by so many metabolic, as well as gastrointestinal troubles in badly burned individuals, that it has been ineffective with deep burns covering more than half of the body.

A number of possible substitutive and restorative means of reducing vaporizational heat loss through the burned skin have been tried and found to be therapeutically inapplicable for various reasons; these are summarized in Table VI.

The first substitutive measure that was tried was the continuous bath with Locke's solution containing phosphate. A 600-liter, stainless steel bathtub, with built-in automatic heat controls and a high-speed microfilter system, was constructed. Patients with full-thickness burns covering 30 to 90 per cent of the body were placed in the bath upon being admitted to the Hartford Burn Unit, and were kept in it until the eschar was all off or until sepsis developed. While in the bath, the burned persons were comfortable. They moved the burned parts freely and painlessly. They ate well and did not lose weight. Basal metabolic rates were near normal. The eschar came off rapidly, bloodlessly, and painlessly. They needed no narcotics or soporifics. Fluid balance was maintained without the oral or intravenous administration of salts other than those contained in the food they ate. However, invasive infections occurred with Pseudomonas py. and other organisms insensitive to

TABLE VI

Means of Reducing Water Flux Through Burned Skin	Reason for Being Unsatisfactory
1. Substitutive measures	
a) covering the burn or burned person's body with water impermeable plastics, spray-on films, and cotton dressings wet with Locke's solution	maceration of eschar with diffuse bacterial colonization, and putrefactive destruction of the eschar and subcutaneous panniculus; sepsis.
b) continuous bath in modified Locke's solution	rapid diffuse bacterial colonization of eschar followed by putrefactive destruction of all tissue down to the enveloping fascia of muscles and periosteum; and sepsis. The rate of production of organisms in one square meter of burned skin with the patient in the bath reached the astronomical levels of about 2.5×10^{11} organisms per square meter per hour.*
2. Restorative measures	
a) impregnating eschar with oleic acid†	condensation of dead dermis into a thin transparent elastic gel (0.3 mm. thick) under which bacteria grew forming confluent abscesses with destruction of subcutaneous panniculus.
b) impregnating top of eschar with petroleum jelly, lanolin, mineral oil‡	maceration of eschar and rapid, diffuse bacterial colonization and destruction of eschar with conversion of partial deep to full-thickness injuries.
c) coating eschar with low melting point paraffins‡	formed films that cracked and lost much of their effectiveness; in addition, bacterial colonization and destruction of the eschar occurred.

* These things could not be prevented by: rapid filtration and sterilization of the bath solution with ultraviolet light or organic iodophores while a burned person was in the bath. Changing the bath solution every 3 to 4 hours, all 450 liters of it, did not prevent them either.

† Stops only the capillary flux of water through eschar (10).

‡ Stops both capillary flux of water and water vapor flux through eschar (10).

antibiotics, most notably: Proteus mir. and morg. These infections developed in the bath and after removal from it while skin grafting was being done (skin grafts could not be applied when the patient was in the bath). The numbers of organisms in the bath were astronomical within a day or two after the burned person was placed in it, although the bath solution was being filtered through microfilters in series with a high capacity ultraviolet liquid sterilizer, and drainage and renewal of the bath solution was performed every four hours. The mean number of organisms per milliliter of bath solution was nearly 5×10^{11}. The inclusion of a concentration of non-absorbable iodophore in the bath solution that quickly sterilized it, after pouring a liter of a 24-hour broth culture of Pseudomonas py. into it, when a patient was not in the bath, effected only a fleeting reduction (1 hour) of the growth of Pseudomonas and other bacteria when a burned person was in it.

The Locke's solution bath did demonstrate a number of things, namely: 1) Burn-wounds are painless at all stages when covered with an isotonic balanced salt solution, having the ionic composition of plasma, except for protein; 2) Electrolyte and water-balance disturbances that occur with burns treated by exposure to air or dry dressings do not occur while the patient is in the bath; 3) The bath reduced the vaporizational and other losses of heat, and the person maintained bodily weight by eating a regular diet while burns covered as much as 60 per cent of the body; 4) Burn eschar could be removed painlessly and bloodlessly without the use of general anesthetics or an operating room.

However, inability to control the growth of pathogenic bacteria in the bath and on the wound obviated all these benefits, and the only thing that was accomplished was to abolish suffering for the time the patient lived before dying of sepsis in the bath, or for the time that the wound was being cleaned of dead tissue before grafting was begun. When grafting was started, the patient had to be removed from the bath, and then pain and suffering began.

Nevertheless, these experiences did lead the way to the development of the methods now being used to prevent sepsis, to remove the eschar without anesthesia and bleeding, to prevent burn-starvation, and to practically free the burned person of pain throughout convalescence. The Locke's solution bath is now an important facet, but not the major part of burn therapy; it is used to hasten eschar separation, to ascertain the number of bacteria growing on a burn-wound, and to provide painless exercise of burned extremities, preventing joint immobilization and disuse atrophy of muscles.

During investigations of factors controlling the rate of movement of water through human skin, dermal capillarity was discovered to be the mechanism responsible for the very rapid outpouring of water and salts through a burn (10). Further research disclosed that adding lipids, including fatty acids, to bared dermis would stop the capillary transfer of water and salt through it, and would convert a wet opaque eschar into a dry translucent one in 24 to 48 hours. After ascertaining these facts from work with human skin taken from fresh cadavers and amputated extremities, oleic acid was sprayed on burns devoid of epithelium in an attempt to restore cutaneous impermeability to water. It produced translucent eschars over full-thickness burns in 24 to 48 hours (Fig. 5), stopped the rapid capillary transit of water and salt through the burn, produced a painless wound, and did not convert superficial-partial to full-thickness injuries. However, bacteria grew in the elastic-gel eschar produced by the fatty acid, and invasive infections occurred, negating the metabolic and other benefits effected by the conversion of water-permeable eschar to a water-impermeable one. This treatment was used in a number of cases (Table XV) before it was abandoned.

Clearly, the growth of pathogenic bacteria in the burned tissue and their invasion of the

FIG. 5. Case L. T. Deep burn of the right leg, 48 hours after injury, treated with oleic acid. The translucency of the eschar is evident. The thrombosed veins beneath the dermis are clearly visible.

body as a whole, constituted the main difficulty that had to be surmounted if excess vaporizational heat loss was to be stopped by practicable means.

Because pathogenic organisms of many kinds are practically always culturable from biopsies of burned skin taken at the time the burned person enters the emergency room (2), an effective and safe means of antisepsis was sought after, recognizing that asepsis likely could not be an applicable method of preventing invasive infection after thermal injury, because contamination had been effected before asepsis could be started.

The hypothetical qualities required of a safe antiseptic to be used on burns were first set out. They are:

I. It must be nontoxic, if absorbable.
II. It must be soluble in water, saline, or lipid, in order that vaporizational heat loss be minimized while antisepsis is being effected.
III. The antiseptic action must be prolonged.
IV. It must not kill viable tissue cells in the wound nor interfere with the proliferation of epidermis, or the taking of skin grafts.
V. It should be nonantigenic.
VI. Resistant strains of pathogenic organisms should not develop during its use.
VII. It should be readily procurable.

In this light, an examination of materials previously used as antiseptics on burns may be summarized as follows:

Phenols and betanaphthol kill normal epidermis, are absorbable and are hepatic and renal poisons.

Soluble inorganic salts of mercury are absorbable and highly toxic.

Organic mercurials are bacteriostatically ineffective on burns.

Picric acid is absorbable and is hepatic, renal and cerebro-toxic.

TABLE VII-A

IN VITRO BACTERIOSTASIS OF THREE SOLUBLE SALTS OF SILVER

Silver Nitrate Silver Acetate and Silver Lactate (Concentration of salts, mEq l.)	Growth: 24 Hours @ 37°C. in Trypticase Soy Broth		Growth: 24 Hours @ 37°C. on Trypticase Soy Agar	
	Pseudomonas pyocyanea	Staphylococcus aureus	Pseudomonas pyocyanea	Staphylococcus aureus
0.6	No growth	$1.5 \times 10^{1} \cdot ml^{-1}$	Normal growth*	Normal growth
3.9	No growth	No growth	Normal growth	Inhibition of growth
6.0	No growth	No growth	Inhibition of growth	Inhibition of growth
7.5	No growth	No growth	Inhibition of growth	Inhibition of growth
15.0	No growth	No growth	No growth	Inhibition of growth
29.4	No growth	No growth	No growth	No growth
58.8	No growth	No growth	No growth	No growth
Control 0.0	$5.5 \times 10^{9} \cdot ml^{-1}$	$2 \times 10^{9} \cdot ml^{-1}$		

* No visible difference between growths on agars upon which the silver salts and no silver salts were placed.

Metallic silver in the form of foil exerted *no* action on bacterial growth (three tests on Pseudomonas pyocyanea and Staphylococcus aureus).

A suspension of silver oxide in water (10 G. per liter) completely inhibited the growth of Staphylococcus aureus, but just visibly inhibited the growth of Pseudomonas pyocyanea.

TABLE VII—B

IN VITRO BACTERIOSTASIS OF COLLOIDAL SILVER IN 0.1 N NaCl

Concentration of Colloidal Silver	Growth: 24 Hours @ 37°C. on Tripticase Soy Agar	
	Pseudomonas pyocyanea	Staphylococcus aureus
1×10^{-5}	Normal growth	Normal growth
1×10^{-4}	Normal growth	Normal growth
1×10^{-3}	Inhibition of growth	No growth
5×10^{-3}	No growth	No growth
1×10^{-2}	No growth	No growth

1×10^{-2} = 1 G Silver in 100 Ml. of saline.

10 per cent silver nitrate is necrotizingly escharotic.

Iodoform is absorbable and toxic.

Antibiotics are antigenic, and resistant strains of organisms arise during their local use.

Soluble sulfonamides are antigenic, and resistant strains of bacteria develop during their local use.

Nitrofurazone is absorbable and ineffectively bacteriostatic for Pseudomonas py. and many other organisms that infect burn-wounds.

Xeroform is bacteriostatically *ineffective* for staphylococci and Pseudomonas pyocyanea.

Dyes (gentian violet, cresyl green, methylene blue, etc.) are bacteriostatically ineffective on deep burns.

However, an examination of the literature pertaining to the antiseptic properties of metals and their salts indicated that the biological effects of atomic silver and its salts upon bacteria and epidermis should be re-examined.

Some of the data relating to *in vitro* testing of the bacteriostatic effectiveness of three soluble salts of silver and colloidal silver are tabulated in Tables VII-A and B. Results of testing the bacteriostatic action of a 0.5% solution of silver nitrate in water upon infected burn-wounds and upon contaminated burn-wounds are shown in Figures 6 and 7 (Cases G. H. and G. S.).

Thick cotton gauze dressings, properly applied, kept continuously wet with a 0.5% aqueous solution of silver nitrate (29.4 mEq. Ag^{+}/1.), and changed once or twice daily, effect bacteriostasis of many species of bacteria on human burn-wounds at all stages. However, on burn-wounds, they are not completely, if at all, bacteriostatic for Paracolon species, Klebsiella and Aerobacter species, and a number of saprophytic organisms culturable from normal human skin. (See Tables IX and X). Nonetheless, they have been highly bacterio-

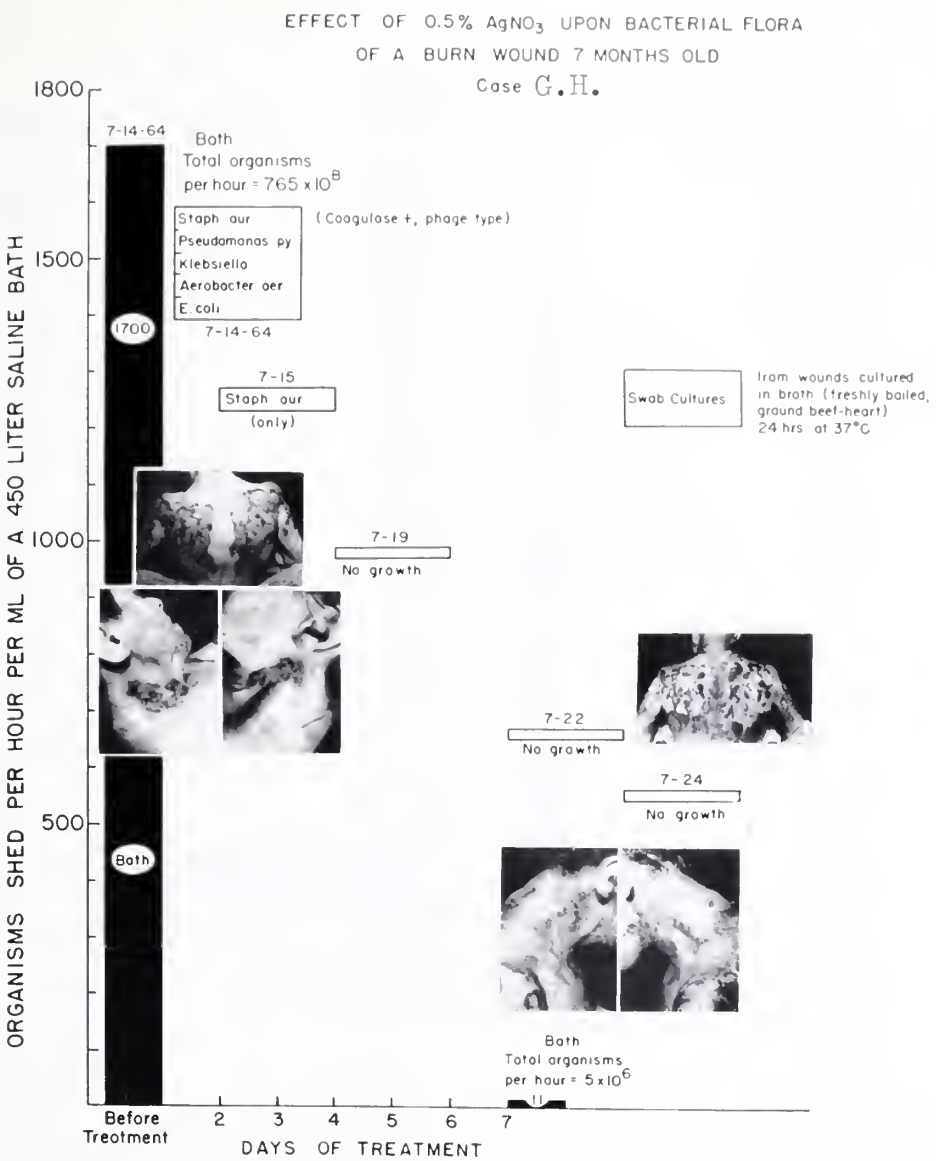

FIG. 6. Results of testing the bacteriostatic action of a 0.5 percent solution of silver nitrate in water upon infected burn-wounds. (Case G. H.)

static for Staphylococcus aureus, hemolytic Streptococci, and for most of the time in almost all cases, for Pseudomonas py. and E. coli. This has been usually so, even when the silver-nitrated dressings have been applied after the wounds have been widely infected and heavily colonized by these bacteria. (Case G. H. is an example of this.) The rate of shedding organisms into a bath containing 450 liters of Locke's solution from a unit area of a deep burn-wound treated with 0.5% silver nitrate from the beginning varies between 1/100th and 1/100,000th of the rate obtaining from a unit of burn surface treated with occlusive dressings, continuous saline baths or with exposure (no dressing). See Table XI and Figure 8.

Septicemia has not occurred with any burn,

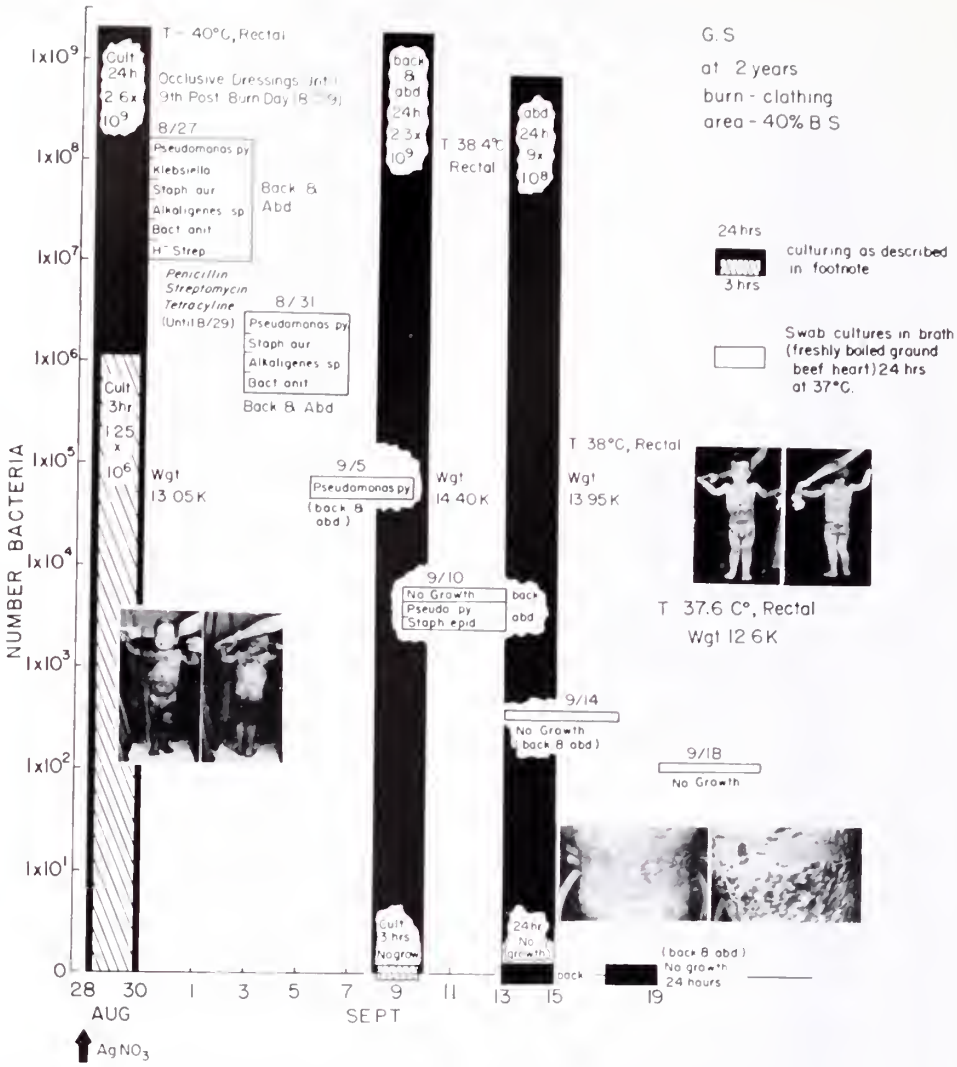

FIG. 7. Results of testing the bacteriostatic action of a 0.5 solution of silver nitrate in water upon contaminated burn-wounds. (Case G. S.)

regardless of size or depth, while silver-nitrated dressings have been used from the start of treatment.

During seven months, in more than 1,300 cultures of burn-wounds, no bacterial strain originally sensitive to 0.5% silver nitrate has become insensitive or resistant to it. A species of Pseudomonas py. has been found once that was relatively insensitive to $AgNO_3$. Its growth on agar was completely inhibited only with 1.0% $AgNO_3$. This organism was found on one burned patient (S. H.) one week after the $AgNO_3$ dressings had been discontinued, and dressings wet with Locke's solution had been substituted; Table X. It has not been met since, during more than 1,100 cultures of burn-wounds.

Although individuals have been admitted to the Hartford Burn Unit with burns heavily infected with Staphylococcus aureus and placed in beds beside burned persons dressed with 0.5% $AgNO_3$, not a single instance of

TABLE VIII

CASE W. B.-HARTFORD BURN UNIT

BACTERIAL COLONIZATION OF BURN WOUND

TREATMENT-EXPOSURE, INTERMITTENT SALINE BATH AND OLEIC ACID—NO $AgNO_3$

Area of Burn. 80% of body surface, 20% deep partial, 60% full thickness. Died—30th post-burn day of sepsis (2nd day of 5th week). Pseudomonas pyocyanea septicemia.

Bacteria	Days							Weeks Post Burn			
	1	2	3	4	5	6	7	2	3	4	5
Pseudomonas pyocyanea			−		−		−	+++	+		+++
Staphylococcus aureus			−		−		++ ++	+	−		+
B. Hemo. Streptococcocus			−		−		++	+	−		−
Proteus mirabilis			−		−		−	++	+		++
Indole⁺ Proteus			−		−		+++ +++	++	+		++
B. anitratum			−		+		++++ ++++	−	−		−
Alcaligenes sp.			−		+		++	−	−		−
Esch. coli			++		+		++ ++	++ ++	+		−
Candida sp.			−		−		−	−	−		−
Paracolon sp.			−		−		−	++	−		+
H.⁻ strep., staph. a. bacillus species			++		+		+++ +++ +++	+++	+		++
Klebsiella Aerobacter sp.			−		−		++ ++	++	+		−
Anaerobes			−		−		+++ +++	+++	+		−
Number of cultures taken			2		1		9	3	1		3

Legend: − organism not grown, + organism grown.

Number of +'s designates number of cultures from which the organism was isolated during a time period; e.g. during 2nd post-burn week 9 cultures were done and anaerobes were found once, Klebsiella, Aerobacter 3 ×, etc.

cross-infection with this organism has occurred. Only one instance of cross-infection with Pseudomonas py. has occurred.

Although 0.5% silver nitrate is effective as a bacteriostatic agent *in vivo* on burn-wounds, and *in vitro* on agar and in broth, nothing is known about the actual chemical state of the silver or its concentration nor the molecular mode of action involved in the process of its bacteriostatic or bactericidal action, *in vivo*.

Under certain circumstances, the concentrations of certain metals, notably silver, requisite to kill bacteria is exceedingly small: 40 gamma of silver per liter being sufficient to sterilize water. (9) In fact, there is evidence that the adsorption of a single silver ion by a bacterium is enough to kill it. (6)

The forms of silver that we have tested against Pseudomonas py. and Staphylococcus aureus, cultured from burn-wounds, and have found to possess bacteriostatic activity against both organisms in low, but higher than oligodynamic concentrations, are: $AgNO_2$, AgCl, Ag_2O, $Ag_3C_6H_5O_7$, $AgC_2H_3O_2$, a number of silver proteinates and colloidal silver.

There is no question but that an aqueous

TABLE IX

CASE D. W.—HARTFORD BURN UNIT

BACTERIAL COLONIZATION OF BURN WOUND

TREATMENT—$AgNO_3$ 0.5% AND INTERMITTENT SALINE BATH

75% body surface burn—40% deep partial, 35% full thickness. Recovered.

Partial gastric resection for bleeding Curling's ulcer on 30th post burn day. Incision made through burn. Convalescence was uncomplicated. He was febrile (temperature above 37.6°C.) twice during 90 post burn days.

Bacteria	Days							Weeks Post Burn							
	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9
Pseudomonas py.		−	−	−		−	−	−	−	−	−	−	−	−	+
Staph. aureus		−	−	−		−	−	+	−	−	−	−	−	−	−
B. Hemo. Strep.		−	−	−		−	−	−	−	−	−	−	−	−	−
Proteus mirab.		−	−	−		−	−	−	−	−	−	−	−	−	−
Ind.' Proteus		−	−	−		−	−	−	−	−	−	−	−	−	−
B. anitratum		−	−	−		−	−	−	−	−	−	−	−	−	−
Alcaligenes sp.		+	−	−		−	−	−	−	−	−	−	−	−	−
Esch. coli		−	−	−		−	−	−	−	−	−	−	−	−	−
Candida sp.		−	−	−		−	−	−	−	−	−	−	−	−	−
Paracolon sp.		−	−	−		−	−	−	−	+	+	++	−	−	−
										++		+			
H.' strep., staph. e.		+++	+	+		+	+	+++	++	+	−	−	−	+	−
bacillus sp.		++						++	++						
								++							
Klebsiella Aerobacter sp.		+	−	−		−	−	++	−	−	−	++	++	−	−
								+							
Serratia marcescens														+	+++
															++
Anaerobes		+	−	−	−	−	−	+	−	−	−	−	−	−	−
Number of cultures taken		5	2	1		4	1	9	9	6	4	5	3	2	5

Legend: − organism not grown; + organism grown.

Number of +'s designates number of cultures from which the organism was isolated during a time period: e.g., during 2nd post-burn week, 9 cultures were done and anaerobes were found once, Klebsiella, Aerobacter 3 ×, etc.

solution $AgNO_3$ (29.4 mEq./l.) does not significantly inhibit the growth of epithelium. Split skin grafts 0.2 to 0.3 mm. thick, cut into pieces 1 to 4 cm.², and placed on granulating wounds, so grow that 20 pieces with a total area of about 80 cm.² proliferate and cover with epidermis a granulating area of about 400 cm.² in 14 to 20 days, while the entire wound is continuously covered by dressings wet with 0.5% $AgNO_3$. Case L. B., Fig. 9, is an example of cutaneous coverage obtained by stamp grafts during 19 days while covered continuously with dressings wet with 0.5% $AgNO_3$.

Bared, non-granulating extensor mechanisms, covering the interphalangeal and metacarpophalangeal joints of the hands, have been covered with split grafts that took over them in entirety when applied between the 20th and 50th post-burn days. All the while, before and after grafting, the burned hand was dressed with silver-nitrated wet dressings. No significant limitation of motion has occurred in any joint so treated. Fig. 10 demonstrates the functional result in such a case.

Donor sites of 0.2 and 0.3 mm. split-skin grafts have been observed repeatedly to heal

TABLE X

CASE S. H.—HARTFORD BURN UNIT

BACTERIAL COLONIZATION OF BURN WOUND

TREATMENT—$AgNO_3$ 0.5% AND INTERMITTENT SALINE BATH

Area of Burn: 40% full thickness, 30% deep partial thickness. Total 70% of body surface.

Bacteria	Days							Weeks Post Burn												
	1	2	3	4	5	6	7	2	3	4	5	6	7	8	9	10	11	12	13	14
Pseudomonas py.		−			−	−		−	−	−	−	−	−	−	−	8+†	++	+++	++	++‡
Staph. aureus		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
B. Hemo. Strep.		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
Proteus mirab.		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
Indole + Proteus		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
B. anitratum		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
Alcaligenes sp.		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
Esch. coli		−			−	−		−	−	−	−	+	−	−	−	++	−	−	−	−
																++				
Candida sp.		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
Paracolon sp.−		−			+	−		12+	11+	12+	+++	+++	−	−	−	−	−	−	−	−
											++									
H. Strep. Staph.		++			−	−		8+	++	8+	+++	+	+	−	−	++	−	+	−	+
a. bacillus sp.		+														++				
Klebsiella		−			−	−		−	−	−	−	+	++	−	−	++	−	−	+	−
Aerobacter sp.													+++			+++				
Serratia mar.		−			−	−		−	−	−	−	−	−	−	−	−	−	−	−	−
Anaerobes		−			−	−		−	−	++	−	−	−	−	−	−	−	−	−	−
Number of cultures taken		4			2	1		18	11	13	11	8	5	1	1	8	2§	3	2	2

* $AgNO_3$ dressing discontinued.

† Sensitive to 0.5% $AgNO_3$.

‡ Organism now sensitive to 1.0% $AgNO_3$ but not to 0.5%.

§ $AgNO_3$ dressing started again.

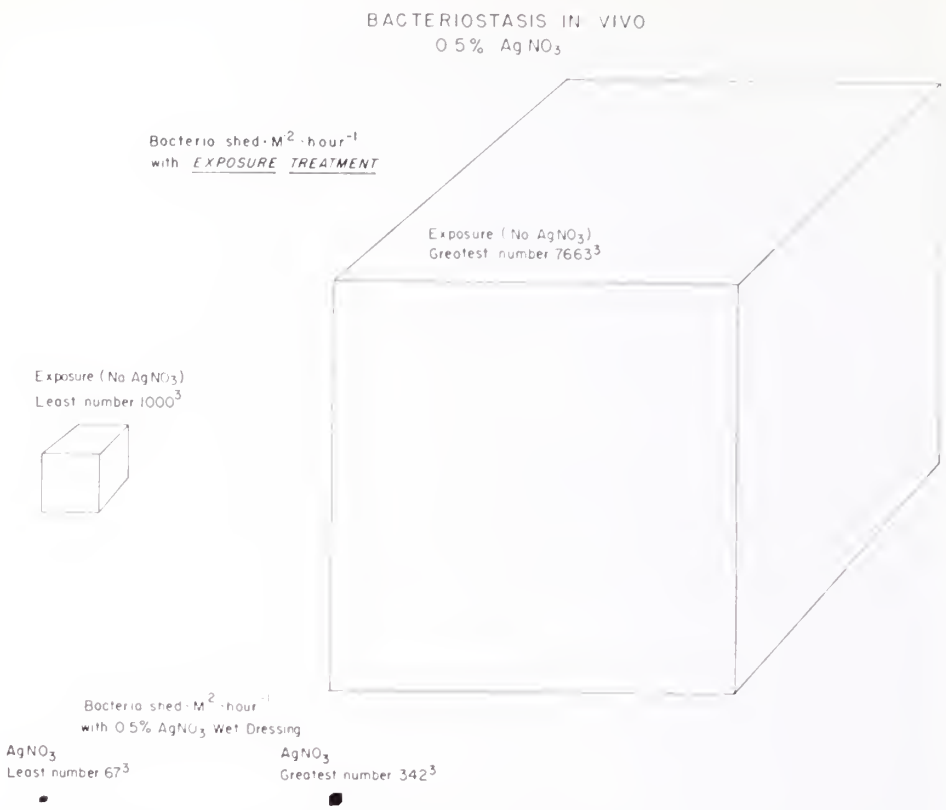

FIG. 8. This is a graphic representation of the upper and lower limits of the numbers of bacteria shed from a burn-wound into 450 liters of Locke's solution during one hour of immersion in the solution. The open cubes at the top delimit the numbers of bacteria coming from burn wounds treated by the methods listed in Table XI. The black cubes below delimit the numbers coming from burn-wounds treated with 0.5% $AgNO_3$. The rates of bacteria-shedding were measured during the 2nd and 3rd post-burn weeks.

promptly under a dressing continuously wet with 0.5% silver nitrate, so that new grafts can be obtained from these very sites in 12 to 14 days (Fig. 11). Should 0.5% silver nitrate have any propensity of injuring mature or growing skin or tendon, it should have been demonstrable under the above particular circumstances of its use.

Nonetheless, the margin between the concentration of $AgNO_3$ that is noninjurious to the skin, and that which is injurious, is narrow. Dressings wet with 1% $AgNO_3$, and placed upon newly-regenerated epidermis of a burn, has *killed* the new, but solid, epidermis in *36 hours*, converting a closed to a shallow, open wound. This same wound healed again in eight days after the concentration of $AgNO_3$ in the dressing was reduced to 0.5%.

In order that 0.5% silver nitrate effect bacteriostasis on a burn-wound, certain conditions must be met.

The dressing that acts as the vehicle of delivery of the silver salt to the burn-wound must contain no impediment to capillarity or diffusion, and must be so thick that it holds a large volume of solution, and it must be in contact with the wound everywhere.

To these ends, a satisfactory dressing consists of six to eight layers of 4-ply, 9-inch dressing gauze, thoroughly wet with solution before its application, and closely coapted to the wound surface by spiralled elastic wrappings of two thicknesses of 6- to 12-inch wide

FIG. 9. Demonstrates the speed of growth of stamp grafts under a dressing continuously wet with 0.5% $AgNO_3$. The photographs show the full-thickness burns of the upper back, back of the head and neck, and shoulders of L. B. These wounds were covered in rough checkerboard fashion by stamp grafts 0.3 mm. thick. The grafts placed upon the left shoulder on March 25, 1964, are visibly stained with silver in the photo taken on March 27. The grafts on the right shoulder and back were put on just before this picture was taken and are practically invisible. Nineteen days later the whole wound was covered by epithelium derived mainly from epithelial proliferation from the stamps. The newly grown epithelium is stained with silver except over the lower left scapula where the stain had been largely removed. The lack of contracture of the skin generated from the stamps is evident in the photograph, taken June 10, 1964. The darkness of the newly grown skin on June 10, 1964, is related entirely to hypervascularity and not to argyria. The upper photograph of Fig. 9 also demonstrates the paleness, thinness, and non-edematous character of the surfaces of clean subdermal tissues that are remarkably capable of graft acceptance and sustenance. These surfaces were free of all bacteria excepting Paracolon species and Klebsiella when the grafting was done.

stockinette cut-on-bias. This dressing complex is kept dripping or almost dripping wet by the addition of 0.5% $AgNO_3$ every three to four hours between the daily changes of dressing.

The person so wetly dressed must be covered with a layer or two of dry cotton sheeting or blanket, in order to minimize evaporation from, and the loss of heat through, the dress-

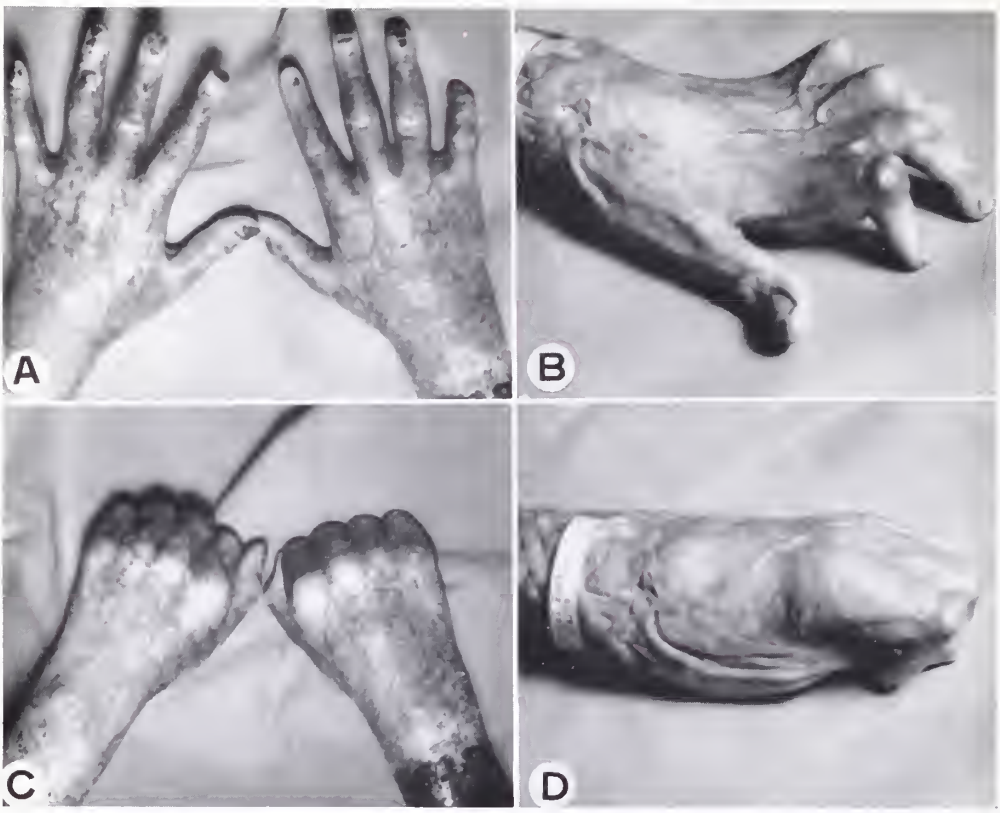

FIG. 10. Case D. W. The photographs A and C demonstrate the lack of deformity and the excellent function of a badly burned hand that was *covered continuously with the silver-nitrated wet dressing.* The eschar was removed from the entire dorsum of the hand on the 14th post-burn day, using surgical debridement during general anesthesia, a procedure that has been abandoned as unnecessary and too destructive of living tissue. During the debridement, the extensor tendons of the first and second fingers were exposed over the metacarpophalangeal joints, and, in the case of the first, over the proximal interphalangeal joint as well. Grafting was delayed by the gastric resection for the bleeding Curling's ulcer until the 34th post-burn day when strips of 0.3 mm. thick autografts were laid upon the bare tendons overlying the above joints. These grafts all took well, and now, four months later, the tendons glide freely under them. There is unrestricted motion in all joints of the hand except the distal interphalangeal joint of the right fifth finger. The hand grip strength is now more than 60 pounds. Photographs B and D, taken 417 days after the injury, show a poor functional result after a deep burn of the dorsum of the hand that was treated with surgical debridement of the eschar followed in five days by the application of sheets of thick split-thickness grafts to the cutaneously-denuded wound. *0.5% aqueous silver nitrate was not used in this case.*

ing. This, these dry top coverings do, regardless of their mesh, by a number of mechanisms.

First, they reduce conductive and convective loss of heat from the body by confining convection currents generated at the dressing surface by the thermal agitation associated with evaporation, and by blocking away those convection and other air currents existing within the room from the surface of the relatively good heat-conductive wet dressing.

Second, the dry covering establishes a heat reservoir between it and the wet dressing (Fig. 12). From this reservoir the heat comes which is absorbed in the vaporization of water at the wet dressing air-under-the-covering interface. The heating of this trapped layer of air to a temperature a degree (F.), and

FIG. 11. Case L. B. demonstrates that 0.5% $AgNO_3$ does not interfere with epithelial regeneration. The photographs show healed donor-sites of split-thickness grafts 0.5 mm. thick taken on the same day with a Brown electric dermatome. All of the photographs were taken 29 days after the grafts were cut. The donor areas shown in A. are located upon the medial and anterior surface of the right thigh. These wounds were covered with dry fine-meshed gauze and an occlusive dressing. The fine-meshed gauze was left in place until it separated spontaneously from the wound surface. The areas shown in B. and C. are located over the antero-medial, anterior and lateral surfaces of the left thigh and the antero-lateral surface of the left leg. The wounds were covered with dry fine-meshed gauze overlain by an occlusive dressing that was changed daily and continuously wet with 0.5% $AgNO_3$ until the fine-meshed gauze dropped off during a saline-bath.

under other environmental circumstances, 4 to 5°F., above that of the outer surface of the wet dressing is explicable. Either one or the other or both of two mechanisms can account for it: either the air saturated with water vapor and trapped between the dry blanket and wet dressing absorbs radiation (infrared) coming from the body beneath, and becomes warmer than the surface of the wet dressing, or the hydratable cotton of the dry sheet or blanket, having a positive heat of wetting, give off heat until they become fully saturated with water vapor. In other words, either radiation coming from the body is absorbed by the wet air and serves as the source of the heat of vaporization of water at the surface of the wet dressing, or the water vapor escaping from the sheet is absorbed by the dry cotton blanket, producing heat of hydration or wetting—or both phenomena occur.

Third, the dry blanket also significantly reduces vaporizational heat loss by another mechanism: it serves as a barrier to the convective removal of water vapor from the surface of the wet dressing. The rate of evaporation from an open beaker is reduced by a half by merely interposing a single layer of filter paper or coarse Marlex fabric between the general air reservoir and the air immediately covering the surface of water contained in the beaker (10).

Fourth, the dry blanket, by virtue of its having a lower thermal conductivity than that of water, serves to reduce conductive loss of heat from the body. Taking the thermal conductivity of the wet gauze dressing to be that of water at 35°C., and assuming the outer surface to be exposed to air, the wet gauze dressing, 2 cm. thick and having the thermal gradient as measured on the burned body (Fig. 12), would conduct 2,500 calories of heat from body to air per square meter per day. The interposition of a dry blanket of cotton, 2 mm. thick with the thermal gradient as meas-

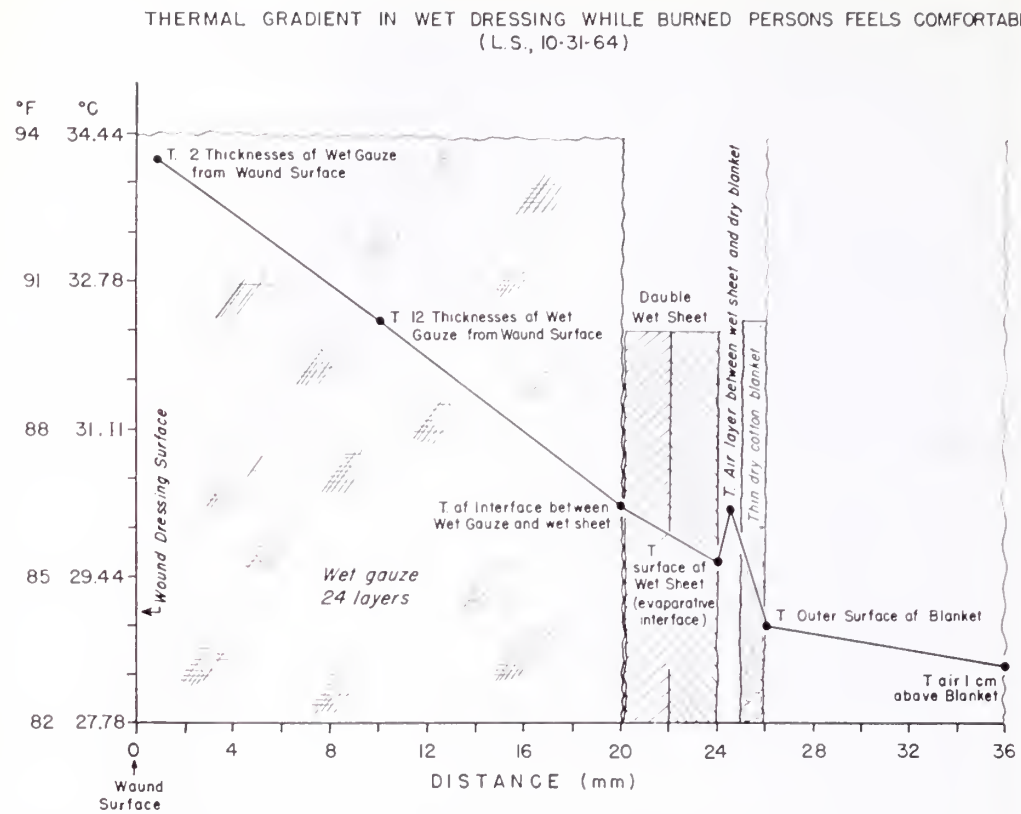

FIG. 12. A graphic representation of the thermal gradients in a wet dressing 2 cm. thick covered by two thicknesses of wet cotton sheet and one thickness of a dry cotton blanket. The temperature of the surface of the wound was 34.5°C. and that of the air in the room was 28°C. The air trapped between the wet sheet and the dry blanket is warmer than the outer surface of the wet sheet. In other cases the temperature of this trapped air-layer has been found to be as much as 3°C. higher than that of the outer surface of the wet sheet. As long as the temperature of this trapped air is higher than that of the surface of the wet sheet from which evaporation takes place, the heat of vaporization comes from the air-layer and not from the person's body. However, let the blanket become wet and the wetly dressed burned person soon complains of being cold. The reasons for this are obvious. When this happens the heat of vaporization must come from the body because the air at the evaporative surface is colder than the wet dressing's surface and the heat must now come from the body. In addition, the wet dressing surface also becomes exposed to convection currents which remarkably hasten the evaporation and heat loss.

ured and shown in the graph, would conductively transfer to the air above it only 800 calories·M^{-2}·day^{-1}.

Fifth, the dry covering entraps humid air in it and under it, and this reduces radiational heat loss from the dressing and body—moist air is a better absorber of infrared radiation than dry air is. *Clearly, the outer layer of the dressing must be dry at all times, in order that the dressing conserve body heat maximally.*

The silver-nitrated wet dressings have conserved body water satisfactorily, Table XII. These data alone do not constitute proof of the dressing's effectiveness in counteracting the excessive cutaneous vaporizational heat loss associated with the loss of cutaneous water impermeability attending the destruction of the lipid water barrier in burned keratin and the epidermal denudation of the burned skin. Actually, the wet dressing might not have decreased vaporizational heat loss from the body at all, while it reduced cutaneous insensible water loss through the burn to normal. Were the wet dressing left exposed to

TABLE XI

EFFECT OF 0.5 PER CENT $AgNO_3$ UPON THE GROWTH OF BACTERIA ON A BURN WOUND

Case (Hartford Burn Unit)	Treatment	Bacteria·M^{-2}·Hour^{-1} from the Wound		% Body Surface Burn		
		Minimum	Maximum	Deep partial thickness*	Full thickness†	Total
R. N.	Exposure and saline bath	1.0×10^9	2.25×10^{10}	15	60	75
L. B.	Exposure and saline bath	2.0×10^{11}	4.5×10^{11}	5	40	45
W. B.	Exposure and saline bath	2.0×10^9	1.5×10^{11}	20	60	80
S. H.	$AgNO_3$ and saline bath	4.5×10^5	4.5×10^6	30	35	65
N. K.	$AgNO_3$‡ and saline bath	1.0×10^6	4.0×10^6	10	36	46
D. W.	$AgNO_3$ and saline bath	$<3.0 \times 10^5$	1.0×10^6	40	35	75

* Deep partial thickness burns are classified as those epithelializing between the 20th and 100th post-burn days *without grafting*. Areas epithelized within 20 days of the injury are *not* counted as a burn wound.

† Requires autografting for wound closure.

‡ Treated with occlusive dressings for 8 days before $AgNO_3$ was begun. Eschar was colonized with Pseudomonas py., Staph. aureus, B. Hemo. strep. Paracolon, Aerobacter, E. coli, Proteus mirabilis, Bact. anitratum, and anaerobes, when $AgNO_3$ treatment was started.

TABLE XII

AVERAGE INSENSIBLE H_2O LOSS WITH VARIOUS TREATMENT METHODS

LITER/DAY = —L

LITER·M^{-2}·HOUR^{-1} = FIGURES IN ( )

Name and Size of Burn	0.5% $AgNO_3$	Continuous Saline Bath	Oleic Acid Impregnation of Eschar	Post Mortem Homografts	Exposure Treatment
L. T.			3.5 L		
40%			(0.1)		
W. G.			4.0 L		
30%			(0.9)		
D. S.			3.4 L		
80%			(0.8)		
L. Bo.		1.0 L			
60–65%		(0.04)			
D. W.	3.75 L				
70%	(0.09)				
L. S.	1.9 L				
85%	(0.05)				
W. H.	0.74 L				
4 days	(0.07)				
60%					
S. H.	1.3 L				
10 yrs.	(0.04)				
60%					
F. B.		0.6 L			8.2 L
20 yrs.					
80%					
I. G.				0.6 L	4.4 L
11 yrs.					
40%					

air, the evaporation of the water from it that had been put in it with the $AgNO_3$ solution would have removed nearly as much heat from the body, as would have been the case, should the water-leaky burn-wound have been exposed to the air, because the temperatures of the exposed surfaces of wet dressings, measured many times, have always been found to be higher than those of ambient air having temperatures up to 90°F. At the same time, the vaporizational water loss through the burned skin, covered only by the wet dressing is always reduced to a very low rate because the water vapor pressure gradient between burned skin and the wet dressing is almost zero, which is not the case when the burn-wound is covered by a dry dressing or none. Where, then, is there proof that the wet dressings, insulated from room air by dry sheets or blankets, reduce the net rate of vaporizational heat loss from a burned person, and thereby serve to minimize the patient's caloric needs? The fact that persons with deep burns covering 30 to 50 per cent of the body, eating no more than a regular hospital diet, and even as little as 1,900 calories a day (Case N. K.), do not lose significant amounts of weight during as much as 100 days of convalescence, is evidence of proof. See Table XIII. Other evidences are the normal

TABLE XIII

Weight Changes During Convalescence from Deep Burns

Dressings Continuously Wet with 0.5% $AgNO_3$ General Diet Only

Case	Age Years	Size of Burn % Body Surface	Weight Kilos		
			Pre-burn	Minimum	Discharge
N. K.	66	46	42	38	41
S. S.	54	30	70	64.5	64.6
S. H.†	11	65	43.6	41	41.4
R. W.	5	31	16.0	16.0	16.0
A. P.	34	60	73	64.5	65.4
D. W.	25	70	99.1	76*	80.0

* Weight 8 days after gastric resection for bleeding Curling's ulcer. Weight was 86.4 kilos before the resection.

† Basal metabolic rates: 3rd week (+9, 21, 13, 27, 13), 4th week (+14, 14), 6th week (+14), 7th week (+19, 15).

basal oxygen consumptions of burned patients measured while the burn-wounds covered as much as 65 per cent of the body. Case S. H., Table XIII is an example. Direct proof can only be obtained with the use of total body calorimetry, facilities for which we do not have. However, the fact that basal oxygen consumptions of badly burned patients are normal, and they either do lose relatively small amounts of weight, or actually gain weight, during convalescence from deep burns covering up to 50 to 60 per cent of the body, is evidence enough to permit the conclusion: *properly constructed, applied, and attended dressings, kept wet continuously with 0.5% $AgNO_3$, effect reductions of the net heat loss and insensible water loss from burned human beings that are sufficient to reduce the caloric and water needs of the burned person to the range of normal.* To be sure, the reduction of bacterial growth on the wound effected by the $AgNO_3$ may play a role in the abolition of the post-burn hypermetabolism, but—it could not effect this, should the dressing not effect a significant net reduction of the accelerated heat loss that is related to the destruction of cutaneous impermeability to water by the epidermal denudation of the dermis or the disappearance of lipids from the keratin after burning.

What has the simultaneous substitution for two functions of the skin, water and bacterial impermeabilities, effected in the treatment of the burned human being? Ultimately, the

TABLE XIV

Treatment: Locke's Bath and Antibiotics

Name	Age	Size of Deep Burn* % Body Surface	Outcome and Cause of Death	Probability of Death from Probits (Ann.Surg. *137*, 1953)
G. A.	63	40	lived	1.00
L. Bo.	6	60	died (sepsis)	.57
R. N.	11	80	died (sepsis)	.92
H. B.	69	90	died (pulmonary injury from smoke)	1.00
V. H.	39	75	died (sepsis)	.88

Expected deaths: 4.37
Deaths: 4

* Burn that heals in 21 days is *not* counted.

Sum of all cases treated in the Locke's Bath

Expected deaths: 7.40
Deaths: 7

Treatment	Expected mortality: . . 82%	(No difference)
Locke's Bath	Mortality: 77%	

TABLE XV

Treatment: Conversion of Eschar to Elastic Gel with Oleic Acid, Antibiotics, and Locke's Bath After 8th Post-Burn Day

Name	Age	Size of Deep Burn* % Body Surface	Outcome and Cause of Death	Probability of Death from Probits (Ann. Surg. *137*, 1953)
D. S.	57	80–85	death (sepsis)	.95
W. B.	22	80	death (sepsis)	.92
W. G.	24	40	lived	.16
L. T.	64	40	death (sepsis)	1.00 (age factor)

Expected deaths: 3.03
Deaths: 3.00

* Burn that heals in 21 days is *not* counted.

assessment of any treatment of burns must rest upon the analysis of mortality rates. Tables XIV, XV, and XVI contain the data that are available now for the analysis of the effect of the continuous silver-nitrated wet dressing upon burn mortality.

Without the dressing, the mortality rate in the Hartford Burn Unit was exactly that expected from the probits derived from U. S. A. burn mortality statistics published in 1953 (Tables XIV and XV). With the use of the silver-nitrated dressing, only three deaths occurred while eight were expected (Table XVI). Counting only those deep burns that covered 40 per cent or more of the body, the use of the silver-nitrated dressing was attended by a mortality of 33%, while on the basis of recent and past experience a mortality of at least 81

TABLE XVI

TREATMENT: $AgNO_3$ (0.5%) WET DRESSINGS AND ANTIBIOTICS INTERMITTENT LOCKE'S SOLUTION BATH

	Name		Age	Size of Deep Burn % Body Surface (Burn That Heals in 21 Days Is Not Counted)	Outcome and Cause of Death	Probability of Death from Probits (Ann. Surg. 137, 1953)
			Treatment begun immediately			
A.	D. W.		25	65	lived	.70
	S. H.		9	70	lived	.80
	K. K.		2	20	lived	.01
	C. St.		22	82	died (potassium deficit)	.92
	W. H.		4 days	60	died (negative thermal load)	.98
	L. S.		18	73	lived	.88
	D. H.		22	55	lived	.44
	S. S.		57	30	lived	.20
					Expected deaths	4.93 (61%)
					Deaths	2.0 (25%)
	Treatment begun after wound infection was established during other primary treatments as designated					
		Previous Treatment				
B.	L. Br.	exposure and baths	22	36	lived	.14
	G. H.	exposure and antibiotics	41	23	lived	.02
	L. H.	Xeroform	13 mos.	90	died (sodium deficit)	.97
	N. K.	Xeroform	66	44	lived	1.00
	G. S.	Mercurochrome and Xeroform	2	22	lived	.06
	R. W.†	Xeroform and Mercurochrome	5	30	lived	.06
	A. P.	Furacin	34	60	lived	.60
					Expected deaths	2.85 (41%)
					Deaths	1.00 (14%)

Total of A and B cases with deep burns larger than 40% of body surface. Expected mortality—81%. Actual mortality—33% (a significant reduction in mortality).

Total A and B (all cases). Expected deaths—7.78. Deaths—3.0.

* Gastric resection performed for bleeding Curling's ulcer on 26th day.

† Septicemia with Escherichia coli at time of transfer to Hartford Burn Unit.

per cent could be predicted. What is just as important, none of the three deaths among the 10 cases was attributable to sepsis, while six of the seven that took place among the nine cases not treated with the silver nitrate were.

Furthermore, all of the deaths in the $AgNO_3$-treated group can be attributed to lack of knowledge concerning the magnitude of the salt deprivation associated with the hypotonic silver-nitrated dressing, and the gravity of the negative vaporizational heat loading attending large deep burns in the newborn. That which was learned from these accidents should enable us to avoid them in the future. Without a doubt, the time has come that one can surely predict that deep burns covering 75 to 90 per cent of the body will soon be no more lethal than deep burns covering 30 per cent of the body surface are today. In fact, should an artificial skin be made that has the physical-chemical functions of human skin, total deep burns may be survived, because skin regenerated over dermal remnants can serve as donor areas. We have used it.

The treatment of the burn-wound with dressings continuously wet with 0.5% silver nitrate, while mineral balance has been maintained, has removed a great deal of conjecture regarding the genesis of burn-illness. The illness attending burns after the period of shock is over, excepting the rare Curling's ulcer, is relatable practically in entirety to infection, to negative vaporizational thermal loading and to mineral imbalances. There is no longer any reason to search for or to impugn any non-bacterial toxin or antigen as cause of burn-sickness or death after deep thermal injuries covering up to 85 per cent of the body.

With the control of invasive infections, negation of negative vaporizational thermal loading, and the prevention of salt imbalance, the lack of illness attending even subdermal (full-thickness) burns that cover as much as 60 per cent of the body is unbelievable until it is seen. Some measure of it can be gained from movie films taken of the actions of burned persons treated with the silver-nitrated dressings and from photos such as those reproduced in Figure 13.

The anemia that always attends large burns is mainly related to infection. Uninfected burn-wounds do not bleed significantly during changes of dressings, and, in the absence of infection, red blood cells are produced at such rates that, with the relatively small blood losses that come with taking grafts, using the Castroviejo instrument, the red blood cell concentration of the burned person is well-maintained throughout convalescence from deep burns covering 30 to 50 per cent of the body without the transfusion of blood. (See Table XVII).

Anemia does attend very large *full-thickness burns*, namely: those covering more than 40 per cent of body surface, but its treatment requires the transfusion of relatively little blood (See Table XVII, Case S. H.). In such cases, serum iron and extracellular iron in bone marrow may practically disappear, although ferrous sulfate is given in seemingly adequate quantity. The reticulocyte count may also be low. After the administration of iron paren-

FIG. 13. Photos A and B demonstrate the state of health and the painless character of deep burn-wounds of the legs and thighs 60 days after the burn. The deep dermal burns of the hands, arms, and shoulders healed between the 30th and 54th post-burn days. Note the degree of mobility and lack of contracture of the healed arms and of the still-unhealed legs. Photo C, the Graph E, and Photo D demonstrate the changes in physical state and wound appearance during 11 days of treatment of a badly-infected burn with 0.5% $AgNO_3$ wet dressings. At the time photo C was taken, Escherichia coli had been grown in large numbers from blood cultures taken before the silver-nitrated wet dressing was started. The changes in temperature and pulse rates during the silver-nitrated dressings are shown in Graph E. Photo D shows the facial and wound appearances after 11 days of silver-nitrated dressings. Photo F demonstrates the facial expression of physical well-being manifested by an 11-year-old girl, 20 days after sustaining a deep burn covering 60 per cent of the body. Photos G and H show the facial expression of well-being demonstrated by an 18-year-old man, one month after sustaining deep burns covering 85% of the body. The depth of injury and its extent is partially shown in Photo G, taken on the 46th post-burn day. All of these burned people recovered. All of them were treated with the silver-nitrated thermo-pack wet dressings.

A
B
C
D
P
C°
170
150
130
110
90
70
50
42
41
40
39
38
37
36
R.W
5 yrs. ♂
Pulse
Temperature
AgNO3
Dressings Started
11
12
13
14
15
16
17
DAY
E
F
G
H

FIG. 13A–H

TABLE XVII

THE RELATIONSHIP OF BLOOD TRANSFUSION, GENERAL ANESTHESIA AND NUMBER OF SKIN GRAFTINGS TO THE METHOD USED IN TREATING DEEP BURNS

Treatment	Case, Age (yrs.), Area of burn, % B.S.	Blood Transfused for Debridement and Skin Grafting—Ml% B.S. Burn	Total Vol. of Blood Transfused for Debridement and Skin Grafting, and Other Reasons as Designated	Hematocrit at Discharge	No. of Gen'l Anesthesias	No. of Skin Grafting Procedures	Outcome and Comments
Oc. Dr.	J. M. 29 27%	185	5,000 S.D. and S.G.	40	14	3	Lived
Oc. Dr., L. Ba.	D. P. 14 30%	117	3,500 S.D. and S.G.	41	15	2	Lived
Oc. Dr.	H. C. 32 18%	222	4,000 S.D. and S.G.	40	10	3	Lived. Profuse bleeding occurred during and after debridement.
L. Ba., Oc. Dr.	M.A. 53 30%	50	1,500 D., S.D. and S.G.	40	2	9	Lived
L. Ba., Oc. Dr.	H. S. 51 40%	238	9,500 D., S.D. and S.G.	35	12	3	Died of sepsis after wounds were covered with autografts.
0.5% $AgNO_3$ wet dressing and intermittent Locke's Bath	N. K. 66 46%	0	0	30	0	4	Lived. (Diabetic and Hypertensive)
	S. S. 54 30%	0	0	40	0	3	Lived
	S. H. 11 65%	15	1,000 D. and S.G.	21	1	9	Lived. (Religion: Jehovah's Witness)
	D. W. 25 70%	0	(9,500) (All for bleeding Curling's ulcer)	40	2*	8	Lived. Surgical debridement of hands is no longer practiced.
	R. W. 5 31%	0 (while in H. B. U.	(2,000) (for treatment of shock and S.D. before transfer to H.B.U.)	39	1†	9	Lived. E. coli bacteremia prompted transfer to H.B.U.
	A. P. 34 60%	0	(1,000) (for treatment of shock before transfer to H.B.U.)	39	2†	3	Lived. Burns covered with nitrofurazone were badly infected.

Legend: H.B.U.—Hartford Burn Unit, S.G.—Skin Grafting, Oc. Dr.—Occlusive Dressing, L. Ba.—Locke's Bath, D.—Debridement with aid of bath without anesthesia, S.D.—Surgical Debridement.

* One for gastrectomy, one for debridement of hands.

† Before transfer.

terally, the reticulocyte count rises 3- to 4-fold in a week. The dermis may be an important normal storage place for iron, because this peculiar anemia does not attend burns covering up to 65 per cent of body surface unless large amounts of dermis are destroyed.

Although wound bacteriostasis with silver nitrate and control of negative thermal loading

have almost abolished many of the complications of burns, acute duodenal ulcer (Curling's ulcer) still occurs. However, this is not as dangerous as it was. Celiotomy may be performed through unhealed burn without complication. Even incised dermis devoid of epidermis will heal per primam when primarily closed by sutures and covered with 0.5% $AgNO_3$ wet dressings. This is interesting biologically—the healing of thermally-injured, but not killed, dermis can proceed without its normal epithelial covering. The case D. W. is a rarity. The burned man recovered from a gastric resection performed for the second exsanguinating hemorrhage from a Curling's ulcer of the duodenum while epithelially-unsurfaced burn-wounds still covered 50 per cent of the body, and the incision had to be made through epidermally-denuded, burned dermis. Not one day of fever followed the resection, and the wound healed *per primam*. All means of medically treating the ulcer were used between the first and second hemorrhages.

The epithelial resurfacing of the full-thickness burn-wounds, in all cases but one (S. H.), has been effected without using homografts of any kind. Homografting and heterografting with fresh or preserved pieces of skin are unnecessary, even in cases of full-thickness and deep partial-thickness burns covering as much as 85 per cent of the body. The continuously wet, silver-nitrated wet dressings do all they can do and more. The three functions served by homo- or heterografting are: the reduction of insensible loss of water, the reduction of hypercatabolism incident to their mitigating the excessive vaporizational heat loss from the open wound, and the production of a painless, uninfected wound. The silver-nitrated wet dressing does all of these things, and it can do them when the wounds are still unfit for the application of any graft, as well as when the wounds are fit. Furthermore, the dressing does this without the wound-mess of the rejection phenomenon. In addition, the dressing is simpler to use: one does not need to seek suitable corpses or desiccate or otherwise preserve skins, or operate a skin bank.

With fair bacteriostasis and prevention of desiccation of the epidermally-denuded, thermally-injured dermis with silver-nitrated wet dressings, eschars involving variable though partial-thicknesses of the dermis are generated over much of a deep flame-burn. These eschars can be removed almost painlessly without anesthesia and without bleeding within one to three weeks after the burn by splitting the escharotic dead outer layer of the dermis away from the living layer of dermis beneath it. (Fig. 14.) This splitting takes place within an avascular zone that contains large numbers of leukocytes and monocytes which, in turn, overlays a layer of dermis containing many young blood vessels. After the splitting of the dead from the living dermis, within 10 to 90 days, epidermal islands rise out of the dermis, grow rapidly and fuse, covering the wound with epidermis between the 30th and 120th post-burn days. This often occurs without macroscopically-visible granulation tissue growing out in appreciable quantity. Pink spots, just visible to the naked eye, often are the only evidence of granulation. (Figure 15). This regenerated epithelium is soon smooth and tough, and the dermis thickens beneath it. Except for some deficit of pigment and lack of hair, practically normal skin is regenerated in the process.

In our experience, the regeneration of a functional, though hairless and pigment-deficient epidermis, over large areas of deep dermal burns did not take place to an appreciable extent before the use of the silver-nitrated wet dressing. However, now, even regeneration of a functional and little-scarred skin often takes place when only the deepest remnants of the dermis, that collectively have the appearance of a very coarse-meshed muslin, remain after removal of the eschar. Heretofore, the removal of these dermal remnants has been a problem, because split-skin grafts would not take upon them and epidermis did not regenerate over them in sufficient quantity to produce functional skin. Under the silver-nitrated dressing, the regeneration of epi-

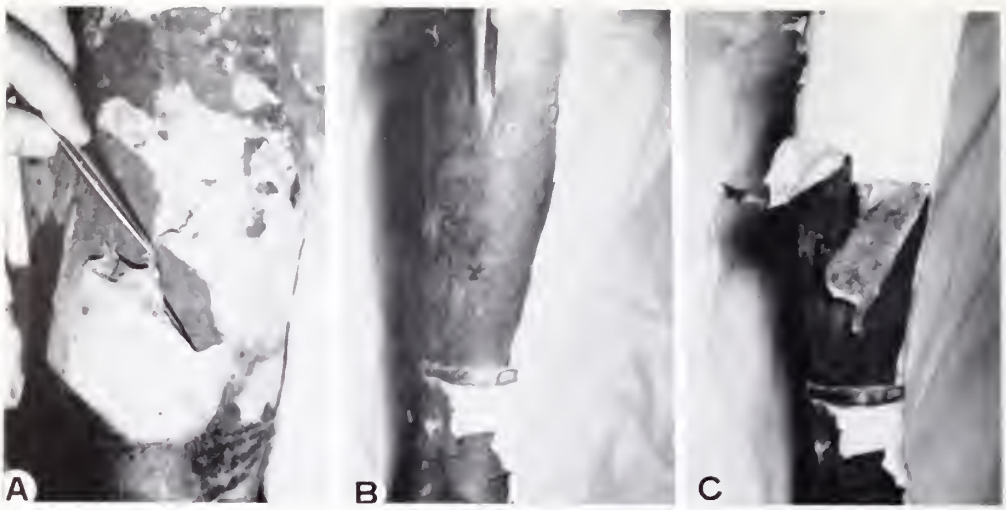

FIG. 14. Demonstrates the bloodless removal of eschar from two deep partial-thickness burns. In both cases the bared, white, deep part of the dermis pictured spontaneously re-epithelized between the 25th and 50th days after taking off the eschar. A. shows the removal of eschar from the distal lateral aspect of the left thigh of S. H. on the 13th post-burn day. B. (case S. S.) demonstrates the splitting of the condensed escharotic outer layer of dermis away from the superficially avascular though living dermis beneath it on the 10th post-burn day. The blade of a forcep was used to make tunnels. In C. the strips of eschar made by incising the roofs of the tunnels are being pulled off. These burns were produced by the burning of a kerosene soaked stocking and pants upon the right leg. The depth of the burn is evident from the amount of the depression of the condensed dermal eschar and living dermis below the surface of the ring of unburned skin around the ankle that underlay the non-flammable elastic web of the top of the stocking.

dermis, after it begins, proceeds over such remnants with remarkable speed. (Fig. 16).

This peculiar regeneration of functional skin from within and upon remnants of dermis during the continuous coverage of a deep flame-burn with 0.5% $AgNO_3$ for 70 to 120 days has effected a remarkable reduction of the amount of expected full-thickness injury that follows the burning of clothing upon the body even when the clothing has been wet with gasoline or kerosene.

In the case of K. K. (Fig. 19), a combined gasoline and clothing burn, there was no full-thickness injury; in that of S. H. (Fig. 17), in which two full layers of cotton clothing were all burned off the body, excepting for the elastic bands contained in it, less than 40 per cent of the injury was full-thickness; in that of D. W. (Fig. 18), the clothing covering the upper trunk was burned off and the hands and face were exposed to flaming sewer gas, but only $\frac{1}{3}$ of the injury was full thickness, and that of D. H. (Fig. 3), the clothing covering the chest and arms was burned off while he ran engulfed in flames *more than 80 feet* before the fire was extinguished by wrapping in a rug, and less than $\frac{1}{20}$ of the injury turned out to be full thickness. In all of these cases, but that of K. K., most of the epidermal regeneration took place upon dermal remnants mainly between the 30th and 100th post-burn days.

In the case of L. S., treated from the first with silver-nitrated wet dressings, the burn was sustained during the prolonged period of time that he was pinioned by a jammed seat belt in a burning automobile from which he was not extricated until the flames had burned the seat belt through—yet, about $\frac{1}{4}$ of the 85 per cent body surface burn resurfaced itself with hairless epithelium between the 40th and 70th post-burn days, and much of this took place over areas where dermal remnants were not visible to the naked eye. When he was admitted to the Unit, he emanated the odor of

FIG. 15. This photograph was taken on the 29th post-burn day. It shows the irregular variations in depth within a flame-clothing burn, as well as some of the characteristics of the healing that takes place under the dressing continuously wet with 0.5% silver nitrate. Area A shows an eschar-like piece of superficial dermal burn that healed between the 14th and 21st post-burn days. It lies in an area of deeper intradermal injury that healed between the 31st and 33rd days. Area B contains small round mesa like islands of regenerated epidermis. These are slightly stained with silver. Three days later these had fused. Areas C contain small volcanic cone-like projections of epidermis. These are the white spots rising out of the basal dermal mesh in which round flat islands of granulation tissue provide the dark contrast. Area D still contains some irregular patches of eschar. Area E is a superficial dermal burn that healed between the 16th and 21st day. Area X is an epidermal burn that healed in 14 days and is deeply stained with silver.

roasted flesh, and the left hand and forearm were lifeless and immobile. Four days after the burn, the left ear and all the skin of the left side of the face were found free of the body in the dressing.

These experiences lead us to conclude that the infliction of a full-thickness burn requiring autografts for epidermal resurfacing, over the extensor surfaces of the body, requires minutes rather than seconds of exposure to the flame of gas or gasoline or the heat of burning clothing, *provided that non-thermal denaturation of dermal collagen by bacteria and by desiccation does not take place.*

With this method of treatment, split autografts of skin take upon structures that are avascular. Bared, non-granulating extensor mechanisms, covering the interphalangeal and metacarpophalangeal joints of the hands, have been covered with split grafts that took over them in entirety when applied between the 20th and 50th post-burn days. All the while, before and after grafting, the burned hand was

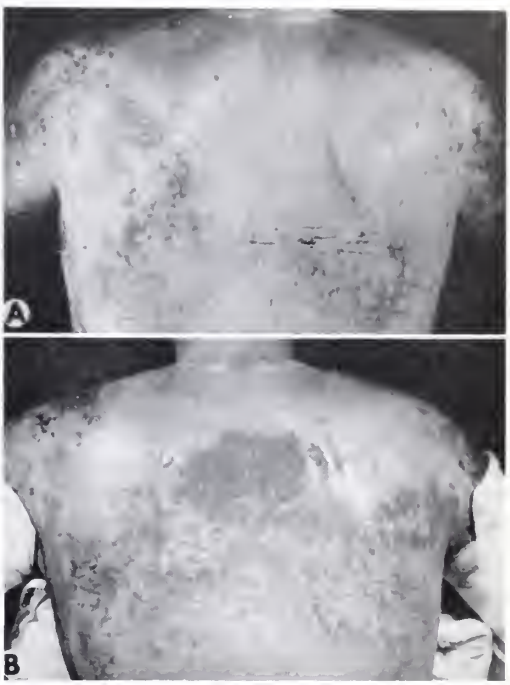

FIG. 16. Case D. W. Photograph B, taken on October 14, 1964, demonstrates healing of the shoulders and patchy granulation tissue over large part of the mid-upper back. Photograph A, taken on October 23, 1964, shows the explosiveness of the epithelial regeneration that often takes place over deep partial thickness granulating burns between the 50th and 100th post-burn days with 0.5% $AgNO_3$. In this case, epithelium solidly covered all of the granulating wounds that existed on October 14, 1964, photo B in only 9 days (99th to 108th days).

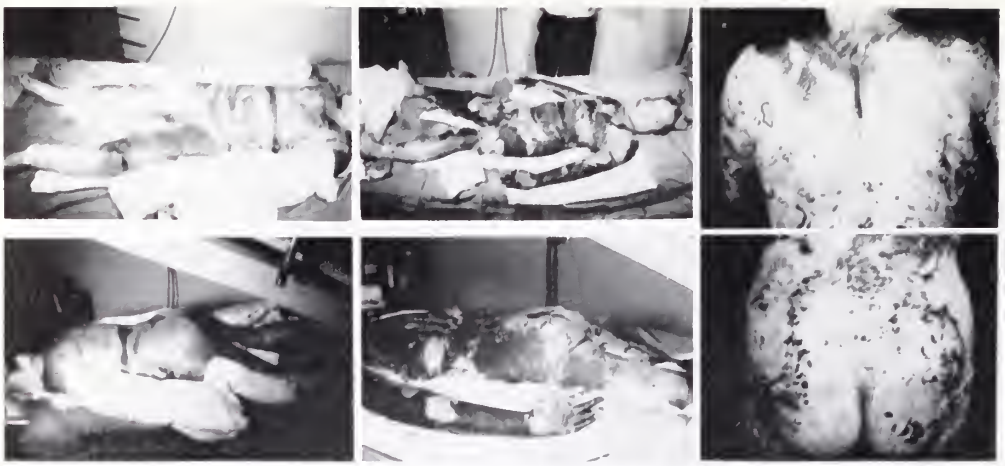

FIG. 17. Case S. H. This is the first instance in which the 0.5% $AgNO_3$ dressings were used in the immediate treatment of large burn wounds. Photo: 4-6-64, was taken on the fourth post burn day. It shows the appearance of deep-partial and full-thickness burns after four days of continuous coverage with the silver nitrated wet dressing. The mons pubis is covered by a deep full-thickness burn and it is not stained. Two strips of unburned skin (protected by non-flammable bands in the clothing) traverse the abdomen, one below and the other above the umbilicus. The entire back is deeply burned. Photo: 4-22-64, shows eschar removed from the mons, parts of both thighs, the left hand, both shoulders and buttocks. The lack of pain and degree of well being are evident from the facial expression. No analgesic had been given before the photograph was taken. Photo: 6-24-64, demonstrates the hairless, pigmentless epidermis that regenerated over the back during 15 days between 6-9-64 and 6-24-64, the 68th and 83rd post-burn days. The flanks, arms and thighs are still devoid of epithelium, and needed grafts to heal them. They are covered at this time only by the pale, thin, painless, non-bleeding granulation tissue that is generated under the silver-nitrated dressing.

dressed with silver-nitrated wet dressings. No significant limitation of motion has occurred in any joint so treated. Figure 10 demonstrates the functional result in such a case. Split skin grafts have also taken on the Achilles and other tendons, after shaving the dried, exposed layer off the tendon with a razor or small electric dermatome.

Although the silver-nitrated dressings benefit the burned patient, they are dangerous. The biologic dangers of the 0.5% $AgNO_3$ wet dressing are theoretically four: argyria, metal toxicity, depletion of body salts and necrobiosis. Argyria is only cosmetically disfiguring. It has not occurred in any case regardless of the size or depth of injury when the silver-nitrated dressings have not covered the mouth. In one case out of 15, there appears to be slight argyria (as yet not proven by biopsy) limited to a burn-wound of the thigh that epithelialized during the time the $AgNO_3$ dressings were being used on the burned lips and chin, and the patient was swallowing some of the dressing liquid. None of the other burn-wounds that covered at least 75 per cent of the body show any evidence of argyria; they all healed with and without skin grafting while 0.5% $AgNO_3$ was applied to them for 130 days. In other words, argyria is a very remote possible consequence of treating burns with 0.5% $AgNO_3$. Evidently silver does not gain access to the circulation in quantity sufficient for argyria when the silver is applied to the burn-wound at any stage.

That argyria does not occur with a significant frequency after the continuous use of dressings wet with 0.5% $AgNO_3$ means that the general toxic potential of silver nitrate as used is non-existent, because even the deposition of enough silver in the body to produce pronounced generalized argyria, produces no detectable physiologic disturbance of the affected organs or of the general health. (8)

Silver salts are poorly absorbed from the

FIG. 18. Case D. W. These photographs show the general physical capacity and nutritional state of a badly burned young adult during convalescence while treated continuously with wet silver-nitrated dressings. Photo: 7-7-64, was taken one day post-burn. Note that a tracheostomy was not performed. Photo: 8-5-64, was taken the 5th day after a partial gastric resection was performed for a bleeding Curling's ulcer. The burn-wounds of the back, shoulders, buttocks, anterior chest, upper abdomen, arms and hands are all still devoid of epithelium. The stitches are still in the abdominal incision which was made through open burn wound. Photo: 9-18-64, shows spontaneous regeneration of skin over the buttocks, lower back, chest and upper abdomen. The incision is well-healed. Stamp grafts taken from the legs and left thigh cover the arms and shoulders.

gastrointestinal tract. The ingestion of 0.1 gram of lunar caustic (95% $AgNO_3$ + 5% $AgCl$) produces no symptoms, and the swallowing of up to 2.5 grams of it in one dose is often harmless, producing at most a gastritis. The lethal oral dose of lunar caustic varies between 10 and 30 grams (11). The chance of a toxic dose of silver being obtained from a dressing wet with 0.5% $AgNO_3$ is practically zero and no signs or symptoms of silver poisoning have appeared in patients almost wholly covered with it for 50 to 150 days.

Depletion of body salts has occurred with the use of this dressing. This is readily explicable

FIG. 19. Gasoline flame burns on the right arm, forearm and hand, (not shown in the early photos) right back and flank, lateral aspect of right thigh and leg, and medial aspect of lower left thigh and upper leg of K. K. treated with dressings continously wet with a 0.5% aqueous solution of $AgNO_3$. The burns were suffered on May 18, 1964. No grafting was necessary. All the wounds had epithelilized spontaneously by June 26, 1964. The lack of scarring is evident in the photo taken August 29, 1964. There is *no contracture of the right arm or wrist.* The child is holding the arm in the position requested by the photographer in order to show the smoothness of the regenerated skin. Photos A, B and C, May 24, 1964. Photo D, August 29, 1964.

and was anticipated, *but the speed of depletion* of the body of sodium salts by the dressing was not expected, because the burn-wound was thought to have a poor exchange surface at least for a few days after the injury (14).

The mechanism of salt abstraction from the body by the dressing is simple: the solution in the dressing is hypotonic (29.4 mEq. $AgNO_3$/ L.).

The salt depletions seen thus far are all explicable on the basis of dressing hypotonicity alone. Biologically-dangerous sodium and chloride deficits with osmolar dilution occur in children having large burns within a matter of a few hours after applying the hypotonic silver-nitrated dressings to the fresh burn. (See Case K. K.). It also occurs, but less slowly, in adults, while the dressing covers 2,500 to 15,000 cm.^{2}

of eschar, or granulating burn-wound when the oral intake of salt and sodium lactate is too small. (See case S. H., 4th week, Table XVIII). Potassium depletion occurs much more slowly, presumably because the K^+ diffusion gradient from the body into the dressing is at most only 5 mEq./l., while that of NaCl is at least 20 times as large. However, K^+ deficit may occur with full-thickness burns covering more than 30 per cent of the body surface within 3 to 10 weeks after the burn, unless adequate K^+ supplements are given. Case C. St. ended fatally because potassium supplements were not given, and the signs of potassium deficit were not recognized until post-mortem review of the case. Since this unfortunate experience, individuals with full-thickness burns covering more than 70 per cent of the body surface have been brought through the whole of a post-burn convalescence without K^+ depletion by properly supplementing the diet with potassium salts. (See case L. S.). Calcium depletion has occurred with *very large deep burns* even during the oral administration of 7.2 grams of calcium lactate daily. (See case L. S. as an example).

So far, magnesium and phosphate deficits have not occurred, at least in recognizable form, although the diets have not been supplemented with them.

The danger of sodium chloride depletion associated with the use of the silver-nitrated dressing is so immediate that the dressing should not be used without very frequent monitoring of serum sodium, chloride and bicarbonate. During the acute phase these analyses must be done every two to four hours in cases of infants and children with burns larger than 10 per cent of body surface, and every six to 12 hours in cases of adults with burns larger than 20 per cent. This frequency of monitoring must be kept up until adequate oral supplementation is possible and then it may be reduced to once daily. *Obviously, microchemical analytic methods must be used or red blood cell deficits from the blood sampling will soon become a serious problem, especially in infants and children.*

At present, a mixture of salts of silver in Locke's solution is being tested for its bacteriostatic action *in vivo*. The *in vitro* tests have shown it to be as effective as 0.5% silver nitrate in water. Should this mixture work *in vivo*, the problem of salt depletion into the dressing will have been solved, and the dressing can be applied safely by anyone anywhere.

CASE REPORTS

Case: A. P., Hartford Burn Unit. A 34-year-old man was transferred to the Hartford Burn Unit six days after he was burned by flaming gasoline. When burned he was barefoot and was clothed only in underclothing. Burns covered both feet, legs, thighs, arms and hands, as well as his face and portions of the trunk and shoulders. (Fig. 13, Photos A and B). The deep burns covered 60 per cent of his body surface, of which five sixths of them were deep partial thickness, the remainder, full thickness. He was given large doses of intravenous penicillin, initially. This was stopped and Mysteclin-F, 2 gm. daily, was administered for two days before transfer. Furacin-impregnated gauze dressings were used to cover all wounds. These had been changed three times under general anesthesia before the time of transfer to the Unit.

On admission to the Burn Unit, the temperature was 39.2°C. He was very ill and complained of pain in all the wounds. All of the dressings were removed. The fetid odor of Pseudomonas py. was all about. He was immediately placed in a bath of Locke's solution to remove the Furacin and to measure the quantity of bacteria on him. 0.5% aqueous silver nitrate dressings were then applied to both lower extremities and 0.5% colloidal silver (in Locke's solution) dressings were applied to the upper extremities, face and trunk. The dressings were changed at least once daily. The fetid odor disappeared in three days. Prostaphlin, 2 gm. daily, and penicillin, 1,000,000 units daily were administered orally. By the 13th post-burn day, more than 95 per cent of the burn eschar had been removed without anesthesia. The removal of the eschar uncovered solid dermis over the arms, neck, back,

TABLE XVIII

CASE S. H. (HARTFORD BURN UNIT)

During Post-Burn Week	Diet	Daily Sodium Salt Supplement, Grams	Post-Burn (Wts.lbs.) (Pre-burn Weight 96 lbs.)	BMR	Subjective Illness	Hematocrit	Serum Na^+	Serum K^+	Serum Cl^-	Debridement	Skin Grafting (Autografts unless otherwise designated.)
1st	Regular	8	115		none	38	125	3.8			
2nd	select	30	109		none	34	123.7	3.7	94.7	begun	
3rd		36	95.5	+9, +21, +13, +27, +13	none	36	131	4.2	87	daily	
4th		7	96.5	+14, +14	Nausea, vomiting for 1 day	41	116*	3.7	88.8	daily	1—good take
5th		31.5	93.0		none	33	140	5	92	*completed*	3 (local anesthesia) 2—good take 1—poor take
6th		28	96	+14	none	31	136	5.2	96	No anesthesia was required and the total blood loss was less than 100 mls. during the removal of all of the eschar.	1—good take
7th		35	93	+19, +15	none	28	139	4.4	84		1—poor take—general anesthesia
8th		32	96		Walking unaided, no illness	21	139	4.8	101		0
9th		22	95.5		Walking unaided, no illness	17†	143	5.2	108		0
10th		22	92		Walking unaided, no illness	15	139	4.2	111		1—homografts from mother
11th		19	91		Walking unaided, no illness	15	134	4.3	108		0
12th		12	90.5		Walking unaided, no illness	15	137	4.2	108	Baths in Locke's solution every 2 to 4 days facilitated removal of eschar.	0—homografts coming off
13th		12	93.5		Walking unaided, no illness	12 transfused (2 units blood)	145	4.1	105		1—good take
14th		32	92.5		Walking unaided, no illness	20	142	4.3	107		1—good take (coverage now 95%)

* Once after 5 days of 7 G. supplement.

† Religious beliefs of parents prohibited the transfusion of blood. A court order was obtained for the transfusion of the liter given during the 13th post-burn week when the anemia reached a level judged to prohibit taking the grafts that were needed. No more blood was needed.

soles, and the anterior surfaces of the legs and thighs. Only patches of dermis remained over the posterior calves and thighs and dorsa of the feet. The patient was in good spirits and did not feel or look ill. The temperature declined gradually during the first seven days on the Unit, and it was normal by the second week and stayed there until discharged. The face was healed by the 21st post-burn day; three days later the right arm and much of the trunk were healed. On the 25th and 31st post-burn day, split-thickness skin grafts, 0.3 mm. thick, were placed on the calves and both popliteal spaces and the dorsum of the left foot. They took well, grew rapidly and fused in three weeks. By the 36th post-burn day, the left arm and hand had nearly healed, and spontaneous healing had occurred over the entire anterior aspects of both thighs and legs and soles of the feet. He was placed in the bath of Locke's solution five times between the 1st and 35th hospital days. The numbers of bacteria shed from the wounds during the baths declined, rapidly reaching 1/100th of the initial within 2 weeks. He received no blood transfusions during the hospital stay, and the hematocrit did not fall below 34%. No general anesthetic was administered while he resided in the Hartford Burn Unit.

Case: L. S., Hartford Burn Unit. An 18-year-old boy was trapped in an overturned, burning automobile by a jammed seat belt and was extracted from the auto seat only after the fire burned the seat belt off. He sustained burns of the entire face, neck, shoulders, both arms and hands, and the entire posterior trunk and the buttocks. Both thighs were burned, save the lateral side of the right one. About ¾ of the legs and feet were burned also. Only the scrotum, a part of the abdomen below the umbilicus, the scalp and parts of the legs and right thigh were not burned. (Fig. 13, photo G). The burns were initially estimated to be 83 per cent of the body surface, with 73 per cent deep partial thickness and full thickness and 10 per cent superficial. This estimate was very nearly correct when burn area was reassessed after all the eschar had been removed. The patient was given 1,000 cc. of physiologic saline intravenously and 100 mg. of meperidine at another hospital, and then transferred to the Hartford Burn Unit, where he arrived about three hours after the injury had occurred.

The pulse was 140 per minute. The temperature was 37°C. At this time, he was restless, vomiting and complaining of inability to move the left arm and hand. The arm was held at 45° of flexion at the left elbow and was board-like to touch from shoulder to the fingertips. The hand and fingers were fixed in extension. An odor of roasted flesh filled the room.

A few milliliters of bloody urine were obtained upon insertion of a catheter; this contained 0.52 gm.% of hemoglobin. The capillary hematocrit was 58%. The serum sodium was 151 mEq./l., the potassium 3.9 mEq./l. A Levin tube was inserted into the stomach. A rapid infusion of Hartmann's solution was begun and the patient started on continuous 0.5% silver nitrate dressings after all of the burned epidermis was removed.

After three hours, the urinary output was 20 ml./h. and the pulse 100. The restlessness and nausea had disappeared. However, the hematocrit rose to 62% during the next 10 hours, but the Hartmann's solution was infused at a rate sufficient *only* to maintain urinary output of at least 25 ml./h., and the rising hematocrit was disregarded. He received 18 liters of lactated-Ringer's during the first 24 hours, and by then he had gained almost 40 pounds of weight. There was marked generalized edema of all burned parts excepting the left hand and arm.

The Levin tube was removed after 24 hours, and after 48 hours he began to eat and drink. The intravenous catheter emplaced through a cut-down, and the urinary catheter were removed at 50 hours. Sodium chloride, from 15 to 30 gm., and molar sodium lactate 60 ml., were added to the diet daily. The facial edema began to subside 72 hours after the burn, concomitant with an increase in the urine output to about 3,000 ml./day. There was little change in the appearance of the left arm, and it re-

mained functionless. Consequently on the 4th day, a long fasciotomy was done over the extensor surface of the forearm. There was no change in the hardness of the forearm nor improved function of the hand, following it.

Digitalis was begun on the 5th day, because of a persistent sinus tachycardia of about 140/min., without there being evidence for oligemia or serious infection as a cause of it.

Debridement of the left forearm on the 6th day showed extensive necrosis of muscle on the volar surface of the forearm, extending from the wrist to the antecubital space. The temperature at this time was above 39°C. The left forearm was disarticulated that day under general anesthesia. The open stump treated with 0.5% silver nitrate dressings. Extensive sharp bloodless debridement was possible beginning on the 7th day and was carried out daily thereafter. The hematocrit had dropped to 30% by the 16th post-burn day. This level was unchanged by administration of 500 ml. of packed red cells and 500 ml. of whole blood in the next five days. By the 11th day his weight had returned to the pre-burn level.

Skin grafting of the face and left arm were begun on the 20th post-burn day after all eschar had been removed without anesthesia assisted by intermittently employing the Locke's solution bath to facilitate the removal. Local anesthesia was used to take the grafts. The temperature, which had dropped to near normal levels 24 hours after the amputation of the left forearm, began to rise in the subsequent five days, and did not return toward normal until the 16th day, after most of the eschar had been removed.

On the 13th day he was tremulous and irritable. The serum calcium was 7.3 mg.%, and the phosphorus, 2.5 mg.%. He had been receiving calcium lactate, 7.2 gm. daily, since the third day. Now, 5.4 gm. calcium gluconate daily were given in addition to the calcium lactate. The signs of hypocalcemia disappeared promptly and eight days later the serum calcium was 9.2 mg.%, and the calcium gluconate alone was discontinued. The hypocalcemia did not recur.

Split-thickness skin grafts, 0.2 to 0.3 ml. thick, were applied to the open wounds twice or three times weekly from the 20th to the 70th day with excellent take of the majority of them. Seven blood transfusions, consisting of either 250 ml. of packed red cells or 500 ml. of whole blood, were given during this time to maintain the hematocrit at 30%. Despite the administration of ferrous gluconate, 1 gm. daily, on the 48th day the serum iron was only 45 μ gm.%, and the total iron binding capacity only 147 μ gm.%. There was no stainable iron in the bone marrow aspirate, which was otherwise normal. The reticulocyte count in the peripheral blood was 1.3%. Five ml. of Imferon were given intramuscularly on the 30th and 31st days. Ten days later the reticulocyte count of the peripheral blood was 9.8%, although the hematocrit had fallen from 30 to 26% during this time.

At present (70th day) 80% of the burns of the trunk are healed. The burns of the right hand and forearm are healed, and about half of the full-thickness burns of the left arm and of the legs are healed. The weight is steady at 121 lbs., and the temperature varies from 37 to 38°C. daily. He is rapidly regaining full function of the right hand. A bare extensor tendon mechanism over the interphalangeal joint of the index finger accepted 0.2 mm. thick skin graft with excellent functional result.

The mental status is excellent. He learned to play chess during the 8th post-burn week. He easily learned self-hypnosis, and this remarkably facilitated his care by nurses and physicians. He has accepted with equanimity the loss of the left arm, and of the left ear, which came off in the dressing together with all of the skin of the left side of the head and face on the 5th post-burn day.

He is now ready for discharge on the 110th post-burn day.

Case: N. K., Hartford Burn Unit. A woman, 66 years of age (diabetic, 12 years; hypertensive, 2 years). On April 8, 1964, at 8:00 a.m., the cotton dress she wore caught fire in the rear at the hem and burned off. Practically none of the area burned, except the popliteal spaces, healed in four weeks. Burns covered 40 to 44 per cent of the body, about one-half of which

was full thickness. Superficial partial burn that healed in 20 days was not counted as injury. The continuous 0.5% $AgNO_3$ wet dressings were begun when she was admitted to the Hartford Burn Unit on the 14th post-burn day. The temperature was then 38.5°C. and the pulse, 136 per minute. The wounds were foul-smelling and wet. Pseudomonas py., Staphylococcus aur., Corynebacteriaceae, the Enterobacteriaceae (Aerobacter, Klebsiella, Proteus mirabilis and morgani, and E. coli) had colonized the eschar. Urinary sugar was 4+ throughout the first 24 hours, although 50 units of insulin were given. Within three days the insulin needed had decreased to 35 units. Glycosuria was rare thereafter.

Within 24 hours after beginning treatment with the 0.5% $AgNO_3$, the temperature fell to 37.4°C., and during the next 11 weeks (76 days), rose above 37.6°C. on 24 days, above 38°C. on 15 days, and never above 38.5°C.

The normal pre-burn weight was 95 pounds clothed; the least weight unclothed during 11 weeks was 92 pounds. The diet during the entire 11 weeks was "diabetic," 1,915 calories (75 gm. fat, 160 gm. protein, 150 gm. CHO), with from 4 to 9 grams of NaCl and 30 ml. of molar Na lactate added, vitamin C, 1,000 mg., multivitamins, twice daily, calcium lactate, 3.75 gm. daily and ferrous gluconate, 1 gm. daily. The only subjective illnesses during the entire 11 weeks were three fecal impactions. Only one blood transfusion (500 ml.) was given on the 1st post-burn day, 11 days before admission to the Hartford Burn Unit. No blood was given afterward, even with four autograftings. The hematocrit, which was 32% when admitted, never fell below 26% and this level was reached during the 9th post-burn week. Then it rose, reaching 31% by the 11th post-burn week. No significant variance in Na^+, Cl^-, HCO_3^-, K^+ or Ca^{++} occurred during 11 weeks. She is well.

Case: D. W., Hartford Burn Unit. A man, aged 25 years, at 10:00 p.m. on July 6, 1964, was burned by the flame of exploding sewer gas in a laundry room. The cotton shirt upon his torso and upper arms was ignited. The force of the explosion was such that it outwardly displaced a wall of the laundry room more than a foot. The heat in the room was intense enough to blister all the paint on the walls and ceiling.

The burn covered between 65 and 70 per cent of the body surface. Of this, 12 per cent was superficial partial thickness (healed in 20 days), 20 per cent was full thickness and 32 to 38 per cent was deep partial thickness burns. The latter healed mainly between the 40th and 90th post-burn days.

Shock was treated with lactated Ringer's solution and 500 ml. of blood. The original weight was 218 pounds; this increased to 257 pounds during the treatment of shock.

All blistered and loose epidermis was removed before the 0.5% $AgNO_3$ wet dressing was applied to the burned surfaces.

The post-burn course was complicated by tracheitis and bronchitis during the first three days and nights. This was treated with Isuprel (1 ml.) and Alevaire (3 ml.) inhalations every six hours. The second complication consisted of two massive hemorrhages from a Curling's ulcer of the duodenum. The first, on the 17th post-burn day, stopped while 3,500 ml. of blood were transfused. The second, on the 26th day, did not stop during the transfusion of 5,000 ml. of blood and a partial gastric resection was performed while 1,000 ml. more of blood were given. The incision was made through unhealed deep partial thickness burn. No post-operative complications occurred, and the wound healed *per primam*. The weight was 191 pounds before the first hemorrhage, 190 before the second and 167 when a regular select diet was resumed 13 days after the gastric resection. Seven days later, the weight was 175 pounds, and there it remained until he was discharged.

The third complication was a sinus tachycardia that at times attained 160 beats per minute. This began six days after the gastric resection. Because neither oligemia or fever coexisted with the tachycardia, full digitalization was accomplished and the tachycardia disappeared within two days.

There were two febrile days (temperature

above 37.6°C.) out of 99, and both of these days were those upon which the gastrointestinal hemorrhages occurred.

The bacteria cultured from the wounds are charted in Table IX.

All of the eschar had been removed by the 24th post-burn day. Autografting of the arms, nose and hands was begun on the 34th post-burn day, having been delayed at least 12 days by the bleeding ulcer and gastric resection. The last grafts were performed on the 100th post-burn day. The removal of the eschar and the skin grafting were done without a general anesthetic and without the transfusion of blood.

The hematocrit was 40% just before the first gastrointestinal hemorrhage, 25% before the second. Seven days after gastric resection it was 44%. The lowest level subsequently attained after seven grafting procedures during 32 days was 38%. No blood was transfused after the gastric resection.

Case: L. Br., Hartford Burn Unit. A woman, aged 22, wife of W. B. (deceased of burns), on February 20, 1964, was burned in the fire which killed her three children and fatally burned her husband. Deep burns covered the head, neck, arms, upper back and shoulders, the right thigh and leg, and the anterior surface of the left thigh (≅36% of the body). Shock was treated in another hospital with 9,000 ml. of saline, 1,000 ml. of blood, and 750 ml. of plasma. Penicillin (2,400,000 units) and streptomycin 1.0 gm. were given daily parenterally for a week and then Staphcillin (500 mgm.) was administered daily from then on. The full-thickness injuries were converted to elastic-gel eschars with oleic acid. For five days all went well; then fever appeared. Saline baths were begun and the eschar removal proceeded rapidly being complete by the 15th post-burn day. The first grafts were emplaced on the 21st day and more on the 28th. The temperature was normal for five days after the first grafting, but then became septic. Pseudomonas py. and Staphylococcus aur. were regularly cultured from the wounds. Because of this and the uncontrolled sepsis leading to the death of her husband, her wounds were dressed with 0.5% silver-nitrated dressings on the 34th post-burn day feeling that no harm could be done. Within three days the signs of sepsis had disappeared and in a week neither Pseudomonas py. or Staphylococcus could be grown from wound cultures. She began to eat well and gained weight. Between the 42nd and 177th post-burn days when she was discharged home alive and all covered with skin, there was no fever; she gained 12 pounds, was given no blood transfusion although seven skin grafting procedures were done. All this while the open wounds and skin grafts and donor sites were dressed with silver nitrated wet dressings.

Case: G. S., Hartford Burn Unit. A boy, 2 years of age, was admitted to a hospital on August 19, 1964, four hours after being burned by a clothing fire set by the explosion of gas in a basement. Superficial partial thickness burns covered about 12 per cent of the body (parts of the face, right arm, part of the left arm, left foot and left thigh, upper thorax and lower abdomen and back); deep partial thickness and full-thickness burns covered 22 per cent of the body (thorax, abdomen, back, and left arm). See Fig. 7. The burned areas were cleaned of loose skin, and fine-meshed vaseline gauze was placed on the burns, which were covered by the standard thick occlusive pressure dressing. Shock was treated with lactated Ringer's solution and blood.

Aqueous penicillin, 928,000 to 2,241,200 units daily, was given parenterally for seven days, and streptomycin, 250 to 1,000 mg. daily, was given for four days. On the sixth and seventh post-burn days, 250 mg. of tetracycline was given parenterally. The bacterial colonization of the wound was as shown in Fig. 7. The temperature varied between 38 and 40.5°C. for the first eight days, and a refrigerated mattress was used (to keep the temperature below 40°C.) for 25 hours during the 5th, 6th, 7th and 8th post-burn days. He was very ill and roentgenographic signs of bilateral lobular pneumonia appeared on the 7th day. The day before, a surgical debridement under general anesthesia had been done and 2% Mercurochrome and Xeroform impregnated gauze

had been put on the wounds. At 4:00 P.M. on the 8th post-burn day he was transferred to the Hartford Burn Unit and a continuous wet 0.5% silver nitrate dressing applied. Within three days the signs of systemic illness had disappeared. The temperature had fallen to 38°C. ±0.4°, rectally, and the numbers of organisms on the wound had decreased to insignificant numbers. The wounds healed rapidly, as shown in Fig. 7.

Case: D. H., Hartford Burn Unit. An 18-year-old boy had his clothes burned off by flaming gasoline on October 28, 1964. The burns covered the face, ears, the anterior neck, the inner surfaces of both arms and forearms, parts of the hands, the entire chest excepting the shoulders and axillae, and the inner surfaces of both thighs. The initial estimate of the burn was 50%, mostly deep-partial and full-thickness. This estimate was erroneous. The burns of the hands, face, ears and most of the back healed between the tenth and twenty-first days. This left only 35 to 40% of the body surface to be counted as burn and only about a third of this was judged to be full-thickness. He was treated in another hospital with occlusive dressings overlying strips of vaselinized gauze. He arrived at the Hartford Burn Unit about three hours after the injury. He had been given sips of water, a tetanus toxoid booster, 5,000 units of tetanus antitoxin, 150 mg. of Meperidine and 100 mg. of Nembutal. He had not urinated since the accident. When admitted to the Hartford Burn Unit, the pulse was 132. He was alert and oriented. The face and arms were grossly edematous. The bladder was empty. Intravenous infusion of modified Hartmann's solution was started. All loose epidermis was removed and 0.5% silver nitrate dressings were applied to all burned areas. In an hour the urine began to flow. During the first 12 hours, 7,750 ml. of Hartmann's solution was given intravenously. The urinary output during this time was 935 ml. The hematocrit on admission was 50%, and within 12 hours it was 58%. The pulse dropped from 132/min. on admission to 112 within 12 hours. From the twelfth to the twentieth hours he received 1175 ml. of Hartmann's solution intravenously, he drank 1750 ml. of $NaCl$-$NaHCO_3$-containing fluid. The urinary output was 475 ml. and the hematocrit rose to 60% but he felt well and could sit up unaided. There were no clinical signs of shock. Twenty-four hours later he was able to stand unassisted and was photographed. He was given Prostaphlin 2 gm./day, Pen VK 1 gm. daily, and Ferrous gluconate 1 gm. daily from admission.

On the second day he was given sodium chloride 12 gm./day and molar sodium lactate 30 ml./day with 15 ml. of Koan three times daily beginning at the 48th hour. The silver nitrate dressings were changed daily and occasionally twice daily in order to facilitate removal of eschar. On the seventh day, he was placed in a bath of Locke's solution to aid in removal of the eschar. Bacterial counts were done at this time. During the first ten days, numerous cultures of the wounds showed only Staphylococcus albus and Diphtheroids. A few cultures taken from unburned skin not covered with silver nitrated dressings contained Staphylococcus aureus and Pseudomonas py. By the fourteenth day, healing was progressing rapidly and the patient was walking and sitting in a chair. The pre-burn weight was 165 lbs. The weight 48 hours after the burn was 180.5 lbs. By the tenth day, it was 159 lbs. It was 141 lbs. the sixteenth day.

Case: W. H., Hartford Burn Unit. A four-day-old boy, who weighed 4.3 Kg., when admitted to the Unit, sustained full and deep, partial thickness burns in a conflagration. These wounds covered the face, the anterior half of the neck, thorax, and abdomen, the volar surfaces of both upper extremities, both hands, the extensor surfaces of both thighs, legs and feet. A passing fireman had picked the child out of a burning orange crate located on the floor of a room engulfed in flames. Originally the injury was estimated to comprise 60 per cent of the body surface, of which deep partial thickness comprised one sixth, and full thickness, the remainder. Shock was successfully treated with 2,675 ml. of lactated Ringer's solution alone, while a gain in body weight of

42 per cent of the original occurred during the first 24 hours. Thick gauze dressings wet with 0.5% silver nitrate were applied to the burned surfaces for 20 minutes out of every two hours. The infant was placed in an Isolette and the ambient temperature kept at 30 to 32°C., with the air nearly saturated with water vapor. Intravenous penicillin and Staphcillin were administered. The hematocrit, which was 65% at admission, was 45% 17 hours later. The serum sodium on the 2nd post-burn day was 142.3 mEq/l. By the 2nd post-burn day, the infant was drinking formula well. The silver nitrate wet dressings were then applied for one half of the day, and after this, the serum sodium fell from 139.5 mEq/l. to 126.4 mEq/l. in eight hours. This prompted a change of treatment of the burn wounds to silver-nitrated wet dressings for 30 minutes every four hours. Within 16 hours, the serum sodium had risen to 142.1 mEq./l. However, on the 4th post-burn day, the serum sodium had dropped again to 126 mEq./l., despite the administration of sodium chloride (3 gm.) and sodium lactate (1½ gm.), orally. However, with no change in treatment schedule, the serum sodium rose to 131.4 mEq./l. by the 7th post-burn day, and it did not fall below this level during the subsequent five days that the infant lived. By the 3rd post-burn day, the child's weight had decreased to 4.8 Kg., after a sustained diuresis during two days. During the whole while the infant lived, he ate, looked and acted well. The wounds were covered by a clean, bluish-black eschar, which was contracting rapidly; the area of eschar was only 60% of the original on the 10th post-burn day. The hematocrit remained between 35 and 37%. The rectal temperature was above 39°C. only once between admission and death. It averaged 38°C. The weight at death was 4.3 Kg. and there was no edema. His death was unexpected by everyone in attendance. It occurred suddenly, with no premonitory signs, 48 hours after he was removed from the Isolette, and subjected to air of a temperature between 78 and 86°F. and of relative humidity between 35 and 50 per cent.

Autopsy disclosed only confluent bronchopneumonia of the right lung, with focal atelectasis and a small right pleural effusion.

The baby's death had many of the features manifested by partially skinned animals kept under environmental conditions similar to those the child was subjected to during the last 48 hours of life. It seems fairly clear that a serious therapeutic error—removal from the controlled environment of high humidity and a relatively high temperature of 32 to 34°C.—played a significant role in the baby's death. Seemingly, an infant upon being burned becomes an artificially premature one in a metabolic sense.

Case: W. G., Hartford Burn Unit. This 24-year-old man was burned on February 3, 1964, in an explosion of paint thinner. He was blown off a platform and fell about 10 feet to a concrete floor with his clothing on fire. Deep partial-thickness burns covered the chest, back, hands, and backs of the thighs and legs, while full-thickness burns covered much of both arms, and superficial burns covered the face.

Shock was treated successfully with Hartmann's solution intravenously and oral salt solution (a total of 16,575 ml. of fluid during 36 hours). He gained 5 kilos of weight, excreted 3.9 kilos of urine and lost 7.5 kilos of water insensibly, of which at least 5 liters escaped through the burns which were exposed to air, except for the wounds of the neck, the latter being covered with gauze wet with a solution of 1.0% neomycin.

During the 6th post-burn day, the large wet wounds of the back were sprayed with oleic acid four times. This dried the wound and the insensible loss of water declined about 800 ml. daily, but still remained at about 2,400 ml. The wounds of the chest, face and arms were not treated with oleic acid. Although he ate well, he lost weight at the rate of almost a pound a day for twenty days. He weighed 156½ lbs. before being burned, and 138 pounds on the 21st post-burn day.

Though 2,400,000 units of procaine penicillin and 1 gram of streptomycin were given daily parenterally for six days and the neomycin wet dressings were continuously applied to the

neck, anaerobic diphtheroids, Staphylococcus aureus, and B+hemo. Streptococci had infected the wounds by the 3rd post-burn day. Because the Staphylococcus was then already insensitive to penicillin and streptomycin, these drugs were discontinued and Prostaphlin (250 mg. 4 × d.) was given. By the 10th post-burn day the Staphylococcus was insensitive to every antibiotic available for testing, and, in addition, Proteus vulgaris was being grown from the wounds; on the 15th day E. coli made its appearance, and on the 30th, Klebsiella grew. The wounds were now the homes of diphtheroids, Staphylococcus aur., B. hemo. Strep. (inconstant), Proteus, E. coli, and Klebsiella.

By the 25th post-burn day, much of the wounds of the back, thighs, legs, face and lower chest were healed and the eschars were off the arms and upper chest and grafting was begun using general anesthesia. Two grafting operations were performed with about 75% take. However, on the 46th post-burn day infection was dissolving the grafts that had taken, although frequently changed dressings wet with 2% neomycin had been applied for five days. Staphylococcus aureus was the predominant organism. On this day the dressings were wet with 0.5% silver nitrate instead of neomycin. Within 48 hours the Staphylococcus aureus had disappeared from the wound, the grafts stopped dissolving and began growing, and he was discharged on the 55th post-burn day healed. Subsequently, broad deep contracting scars developed where the arms were most affected by the staphylococcic infection. These fixed both elbows at 45° of flexion. They were excised and the defects covered with split grafts which were immediately covered with a silver-nitrated dressing. These grafts took in entirety, and the contractures are cured.

This was the first case in which $AgNO_3$ was used to treat a staphylococcal infection affecting a large wound surface. The saline bath was not used because the wound impregnated with oleic acid did not become infected and healed without scar; but so did the legs and thighs and lower chest, which were not treated with the acid. The neck and upper chest, treated early with topical neomycin, were infected with Staphylococcus, and are now patchily thickly scarred. The arms that became badly infected while being treated with only the neomycin are badly scarred by low keloids.

Case: G. H., Hartford Burn Unit. A 41-year-old woman had suffered deep thermal burns of the face, neck, arms, shoulders and back, six and one-half months before admission to the Hartford Burn Unit. The face and arms had been successfully covered with split-thickness skin grafts one month after the burns, but, in the ensuing five and one-half months, seven different attempts to graft the shoulders, back and infra-aural regions of the neck had all been unsuccessful, the grafts dissolving after an initial period of apparent take. Staphylococcus aureus was cultured from the unhealed wounds just before transfer. She received penicillin for the first three days of the illness, but no other antibiotics afterward.

At the time of admission to the Hartford Burn Unit, she was a pale, ill-appearing woman, complaining bitterly of fatigue. The unhealed wounds (Fig. 6) of the back, shoulders and neck were extensively involved by exuberant encrustative pyoderma, and covered with a gelatinous mucopurulent exudate. There was pitting edema of the feet and legs. The lower lip was everted by scar contracture. The hematocrit was 24%. Swab cultures of the wounds grew Staphylococcus aureus, Pseudomonas pyocyanea, E. coli, Aerobacter aerogenes, and Klebsiella pneumoniae. Many of the skin grafts on the back and shoulders were sloughing.

She was placed in a bath containing Locke's solution, and quantitative bacterial counts were done. Continuous wet dressings of 0.5% silver nitrate were then begun. She was allowed to walk the ward or lie in bed, as she desired. Prostaphlin, 1.0 gm./day, penicillin, 1 × 106 units/day, and ferrous gluconate, 1.0 gm./day, were given orally and continued during hospitalization. After 24 hours, she was much improved. The $AgNO_3$ dressings were reapplied. Forty-eight hours later, split-thickness skin grafts, 0.2 mm. thick, cut into one to three

centimeter square fragments, were placed so as to cover most of the unhealed areas, using local anesthesia and a small electric dermatome (Castroviejo) to take the grafts. The silver nitrate dressings were immediately resumed after grafting. The donor sites were also dressed with gauze continuously soaked in silver nitrate. Two days later, the coarse-meshed gauze dressings were removed. Ninety per cent of the skin grafts were firmly in place. Forty-eight hours later, and again five days later, the small open wounds remaining were grafted, with complete take of the grafts. Quantitative bacterial counts in the saline bath were obtained eight days after the initial ones had been obtained. Figure 6 shows the wounds and their bacterial flora during treatment. The eversion of the lip was corrected by excision of scar and split-skin grafting of the cutaneous defect on the chin. She was discharged on the 19th day with only a few very small wounds on the back and shoulders being unhealed.

The hematocrit had risen from 24% on admission to 40% at discharge. No blood transfusion was given.

Case: C. St., Hartford Burn Unit. A married woman, 22 years of age, was burned over 82 to 85 per cent of the body by a propane gas explosion; her nightgown burned off. The distribution of the types of injury determined after her death on the 41st post-burn day was: full-thickness injuries covered 36 to 40 per cent of the body surface, deep partial thickness, 30 per cent, and superficial partial thickness the remainder. The wounds had been dressed in another hospital with gauze heavily coated with vasline, setting the stage for the first technical error: our failure to remove the vaseline with a proper hydrocarbon solvent. Shock was easily treated with lactated Ringer's solution—13 liters were given intravenously, and four liters of salted fluid orally during 36 hours. Although the wounds were well covered with the 0.5% $AgNO_3$ wet dressings, the temperature rose steadily from the 3rd to the 7th post-burn days, when a probing examination of the wounds disclosed a complete liquifactional separation of the greased burned epidermis from the dermis, which had not been removed before the $AgNO_3$ dressings were applied. This epidermis was now removed and during this maneuver a fetid odor filled the room. Many intradermal abscesses, 2 to 8 mm. in diameter, were unroofed in the process. Immediately after removal of the vaseline-greased, dead epidermis from the dead and living dermis beneath it, the temperature fell to normal, although very large numbers of many varieties of pathogenic organisms were cultured from the wounds. The number of organisms coming from a meter^2 of wound was 1.35×10^{10}, 1.8×10^8, and 1.6×10^9 per hour during the 3rd, 4th and 5th post-burn weeks, respectively.

After the 3rd day she ate well, felt well and slept well during the entire post-burn period. Her weight before being burned was 131 pounds; the last weight six days before death was 126.5 pounds. Large dietary supplements of vitamins, sodium chloride, and lactate and calcium lactate were administered daily, *but potassium salts were not.*

A certain cause of death was not found at necropsy. However, a case review disclosed the following: 1) she had not eaten much meat; 2) she complained of weakness for six days before death; 3) she talked much and purposelessly at intervals for three days; 4) the serum chloride had been between 70 and 80 mEq./l., the bicarbonate between 32 and 36 mEq./l., the sodium, between 130 and 136 mEq./l. and the potassium, between 3.6 and 4 mEq./l., for a week before death. In addition, the administration of 0.1 N sodium chloride intravenously had not effected any sustained decrease in serum HCO_3^- concentration. All these things add up to: *chronic severe progressive potassium depletion.* She had not been given supplementary potassium salts to make up for the steady drain of these into the hypotonic wet silver nitrate dressing through the very large wound!

Case: K. K., Children's Hospital, St. Louis. A girl, two years of age, was burned by the explosion of gasoline in a closed space, a basement, at 10:00 A.M., on May 18, 1964.

The areas burned were the right half of the face, the entire right arm, the anterior and

lateral aspects of the right thigh and leg and the anterior medial aspect of the left leg, in all, approximating 18 to 22 per cent of the body's surface. Excepting the more superficial burn of the face, they were all deep partial thickness burns. (See Fig. 19, Photos A, B and C.)

All blistered and loose epidermis was removed, and all wounds, excepting those of the face, were dressed with a thick gauze dressing wet with a 0.5% solution of silver nitrate in water. The facial injury was not dressed.

Hartmann's solution (lactated-Ringer's solution), 1,000 ml. intravenously, and 1,000 ml. of ½-strength Ringer's solution subcutaneously, were given during the first 36 post-burn hours.

Prostaphlin, 250 mg., was administered intramuscularly every six hours.

A biochemical complication of the wet dressing occurred: hyponatremia. The serum Na^+ fell to 126 mEq./l. by the 23rd post-burn hour, and 118 mEq./l. by the 29th. This was corrected in 18 hours by giving 400 ml. of Ringer's lactate solution and leaving the wet 0.5% $AgNO_3$ dressing in place for only 15 minutes out of every hour until the 4th post-burn day. After this, although the wet dressings were then continuously applied, ingestion of one gram of NaCl and 10 ml. of molar sodium lactate every eight hours until the wounds were healed maintained the serum Na concentration between 132 and 142 mEq./l.

Case: S. H., Hartford Burn Unit. A girl, 9 years and 11 months of age, while home alone on the evening of April 2, 1964, had the cotton dress and underwear burned off her body. The dress was ignited at the hem by an open gas flame. A deep partial thickness burn covered 30% of the body, and full-thickness burn 40%. The superficial partial thickness injury that healed within 20 days covered about 8% of the body but is not counted as significant and is disregarded. Shock was profound in two hours and was treated successfully with six liters of lactated Ringer's solution and two liters of oral Locke's solution during 24 hours. No plasma, blood or dextran was given. During the next 24 hours two liters of lactated Ringer's solution were given intravenously. Thereafter she ate a general diet, drank water at will and ingested sodium salts, as recorded in Table XVIII.

Except for one day during the fourth post-burn week, there were no gastrointestinal upsets or complaints. On this exceptional day there were nausea, vomiting and abdominal cramps associated with a serum sodium concentration of 118 mEq./l. For the four days preceding this, only 9 grams of supplementary sodium salts had been given daily. After giving 500 ml. of 2.5% NaCl and 1,000 ml. of 0.9% NaCl solutions intravenously, the symptoms disappeared and did not recur. Aside from this, the child was not ill, needed no opiates or soporifics for pain or sleep, was given only one general anesthetic for the fourth and most extensive autografting, and had one transfusion of a liter of blood given to her before the fifth autografting at the end of the 13th post-burn week.

Upon being queried, on the 105th post-burn day, as to how much better she felt now that the wounds were practically all healed, she answered, "Why, I wasn't sick! I was just burned!"

All wounds were solidly resurfaced with epidermis after five and one-half months, and she was attending school full-time without any seriously disabling contracture. Figure 17 and Tables X, XI show the salient features of the bacterial growth on the wounds, and the extent of the wounds.

The silver-nitrated dressing was discontinued at the end of the 9th post-burn week, because it was felt that the $AgNO_3$ may have been a cause of the anemia. It was restarted seven days later, after Pseudomonas pyocyanea and E. coli had colonized the wounds for the first time.

Case: R. W., Hartford Burn Unit. A 5-year-old boy sustained deep burns covering 30 per cent of his body surface when, while playing with matches, his clothing ignited. He was treated at another hospital with three units of blood and three units of plasma. Ten days later, he was transferred to a second hospital for further care. At that hospital, he was given an

additional 250 ml. of whole blood and parenteral penicillin. The day after transfer, extensive debridement was done in the operating room under general anesthesia. 250 ml. more of whole blood were given as well as oral tetracycline. His temperature rose to 40.5°C. in the next 18 hours and he was transferred to the Hartford Burn Unit. Cultures of the blood then showed E. coli. At the time of admission to the Hartford Burn Unit, the temperature was 40.5°C., the pulse 160. The child appeared ill. Deep burns covered the lower cheeks, the chin, the anterior neck and shoulders, the anterior trunk, the left parts of the left arm and forearm and parts of both arms and forearms, (Fig. 13, Photos C and D). There was phlebitis in the right leg at the site of a saphenous intravenous infusion. Bulky occlusive dressings were removed. Continuous 0.5% silver nitrate dressings were started. Sodium chloride, 8 gm./day. sodium lactate, 1 molar 40 ml./day, and Kaon, 15 ml./day were started. Aqueous penicillin 4,000,000 units and 1 gram staphcillin were given intravenously. Prostaphlin 1 gm./daily and Pen VK 1 gm./daily were begun orally. The patient's temperature record is reproduced in Fig. 13. Organisms cultured at the time of admission to the Burn Unit were Pseudomonas py., Proteus mirabilis, E. coli, Paracolon sp., and organisms of Klebsiella-aerobacter sp. Within 5 days, the wounds appeared much cleaner and on the 6th day, split thickness skin grafts were applied to the face and shoulders with excellent take. More skin grafts were applied with excellent take on the 8th, 13th, 20th, 23rd, 28th and 31st days. The patient, too weak to walk at the time of admission, was apparently well and afebrile after 10 days of treatment. He was able to walk about the ward freely. His hematocrit rose from 33% on admission to 39% on discharge with the administration of ferrous gluconate only. By the 5th post-burn week, Pseudomonas had disappeared from swab cultures from the wound. Spontaneous healing proceeded rapidly from this time and he was discharged on the 60th day with healed wounds.

SUMMARY AND CONCLUSIONS

The magnitude of the respective roles played by reduction of vaporizational negative thermal load and bacteriostasis in the remarkable amelioration of burn illness effected by dressing the wounds with gauze continuously wet with 0.5% aqueous solutions of $AgNO_3$ cannot be ascertained. However, certain things are clear.

1. Ascription of biologic significance to burn toxins or autoantigens is baseless. There is little evident illness after shock is over, even with full-thickness burns covering as much as 80 per cent of the body's surface, when excess vaporizational heat loss, electrolyte imbalance, and bacterial colonization of the wound are prevented reasonably well.

2. The so-called obligatory or stress hypercatabolism attendant upon large burns is *not* obligatory, nor is it relatable to ill-defined endocrinal disturbances (stress) obtaining after injury. When the net vaporizational heat losses and wound infections are *kept small* with biologically appropriate dressings, bodily weight is maintained after deep burns covering as much as 40 per cent of body surface by the eating of a diet containing as little as 1,900 Calories daily. Under these same circumstances, the eating of a regular hospital diet *ad libitum* is sufficient to maintain bodily weight within 10 to 15 per cent of the pre-burn one during more than 100 days required to epithelially resurface the wounds of deep burns covering as much as 65 per cent of the body. During the time the open wounds cover as much as 50 per cent of the body, the basal oxygen consumption usually is not elevated significantly when the silver-nitrated wet dressings are used.

The alleviation of the hypercatabolism associated with large burns is relatable to the particulars of construction and of handling the dressing wet with 0.5% $AgNO_3$. The continuous covering of the wet dressing with a layer of dry fabric reduces the negative thermal loading relatable to vaporization enough to all but abolish the super-normal vaporizational heat loss attendant upon the destruction of the cu-

taneous water barrier by the injury. In addition, the changing of the silver-nitrated dressing daily, largely prevents infection and the hypercatabolism that is relatable to it.

The dressing serves the physiologic and bacteriologic purposes of skin sufficiently well so that homografting or heterografting are unnecessary, even with full-thickness burns covering more than 50 per cent of the body. The dressing does all that homografts can do without the mess of the rejection phenomenon or the bleeding associated with homograft removal before rejection.

An aqueous solution of silver nitrate (0.5% or 29.4 mEq./l.) is an effective bacteriostatic agent *in vitro*, and on burn-wounds *in vivo*, when used to wet thick gauze dressings containing no impediment to diffusion and capillarity. It is non-toxic to man, and argyria does not occur during or after its continuous application to burn-wounds for as long as a hundred and twenty days.

At this concentration, silver nitrate approaches the ideal antiseptic; it prevents the growth of such bacteria as Staphylococcus aur., Pseudomonas py., B. hemolytic Streptococci and E. coli on the burn-wound, and it does not measurably interfere with epidermal proliferation. The range of concentration in which silver nitrate operates this way is narrow. A 1% aqueous solution of silver nitrate kills newly-grown epidermis and a 0.1% solution is not bacteriostatic *in vivo* on burn-wounds. A 0.5% solution of silver nitrate is not bacteriostatic for Paracolon species, Klebsiella, and a number of cutaneous saprophytes *in vitro* and *in vivo*.

The wound surface must be cleared of all diffusion barriers, such as greases and dead epidermis, and later of thermally denatured (dead) dermis, if bacteriostasis is to be obtained and maintained with 0.5% $AgNO_3$. With the exercise of minimal aseptic precautions no infections or cross-infections with Staphylococcus aur. have occurred in any burn-wound treated with the silver-nitrated wet dressing. *One cross-infection* with Pseudomonas py. has occurred. No isolation of the uninfected patients in the Burn Unit from badly infected burned patients admitted to the Unit has been practiced. No filtration, mechanical exchange, or ultraviolet sterilization of the air was used. The dressings were not sterilized with heat before being wet with the silver nitrate solution and applied to the wounds.

With the use of such dressings, and baths in Locke's solution for two to four hours once to three times weekly, deep burns covering as much as 85 per cent of the body can be cleared of eschar by the 20th post-burn day painlessly, bloodlessly and without the removal of living tissues. No anesthesia is required to do this. The uninfected deep burn is relatively painless for a month or more. Excision of eschar during anesthesia is unnecessary, and is too destructive of living tissue to be used, except for deep electric burns.

Provided that the burn is not desiccated or infected, very large parts of a wound produced by the burning of cotton clothing upon the body, even when wet with gasoline or kerosene, will heal smoothly without skin grafting. This spontaneous healing of very deep dermal injuries by epidermis rising out of the depths of dermal remnants may take place with remarkable speed anytime between the 50th and 110th post-burn days. Such regenerated skin is not atrophic and it is not as scarred or contracted as is that epithelium regenerated from unburned skin around the margin of a burn-wound.

With using the Castroviejo dermatome for taking thin autografts, and with covering the donor sites immediately and continuously with silver-nitrated wet dressing, skin grafts 0.3 mm. thick may be taken every 18 to 20 days from the same area. As many as four crops of skin have been taken from the same site during 80 days without a single donor area suffering any full-thickness injury. These thin grafts, placed on uninfected granulations and covered continuously with the silver-nitrated dressing, grow into practically normal skin that is the equal cosmetically and functionally to the resurfacing effected by much thicker grafts.

The cutting of 0.3 mm. thick strips of graft taken with the Castroviejo instrument into pieces 3 to 6 cm.^{2}, placing them in checkerboard fashion a centimeter or two apart upon uninfected granulation tissue and then covering them with the silver-nitrated dressing, rapidly effect solid cutaneous coverage of full-thickness burns. The skin produced is good and at times is practically normal.

With the above techniques, full-thickness burns covering 40 to 75 per cent of the body have been completely resurfaced in 70 to 100 days from such limited donor sites as the legs below the knees, or the lateral aspects of one leg, thigh and flank.

These thin grafts take permanently upon tendons, periosteum, galea and perichondrium that have been covered continuously with the silver-nitrated dressing from the day of the injury. The functional results have been excellent. Hands so badly burned as to bare the extensor tendon mechanisms over metacarpal and interphalangeal joints have been so little scarred that normal function has been easily regained after resurfacing the injuries with the thin skin grafts and keeping them covered with the silver-nitrated dressing until the cutaneous coverage is complete and solid.

The whole of the successful treatment of deep burns covering as much as 50 per cent of the body can be regularly accomplished without the transfusion of blood or plasma, or the infusion of plasma expanders, without a general anesthetic being given, and without the use of an operating room.

Without infection and without excisional removal of eschar, significant anemia only attends deep burns covering more than 50% of the body surface, and then only when the full-thickness injury covers more than thirty per cent of body surface. In such cases the anemia is relatively easily treated.

Without infection the psychiatric disturbances associated with burns covering as much as 85 per cent of the body are few and easy to treat.

With appropriate treatment of shock, the continuous silver-nitrated wet dressings, intermittent bathing in Locke's solution, the non-excisional removal of eschar, and methods of grafting described, the mortality rate has been only 33% in a series of deep thermal burns[7] covering 40 to 90% of body surface, when a mortality rate of 81% was to be expected. None of the deaths were attributable to sepsis. All of them were relatable to metabolic derangements attributable to inexperience with the method of treatment.

Complicated Curling's ulcer of the duodenum does occur with large burns, even though infection and hypermetabolism are circumvented. A case of massively-bleeding Curling's ulcer treated successfully with gastric resection is recorded. The incision was made through burned abdominal skin devoid of epithelium and still the wound healed *per primam*. The convalescence from the burns covering 60% of the body proceeded without a single day of fever during the eighty days needed to resurface the injuries after the gastric resection. This case proved that dermis is capable of healing while uncovered by epidermis, provided that infection and desiccation do not affect it.

The dressing wet with a 0.5% aqueous solution of $AgNO_3$ is dangerous! Mainly because of the hypotonicity of this solution (29 mEq./l.), the dressing wet with it becomes a sink into which the diffusable mineral constituents of the body move through the burn-wounds.

Sodium depletion, having such an origin, was one main cause of death in one case, and potassium depletion in another.

Shock associated with deep burns[8] covering 30 to 85% of the bodies of 10 patients has been treated successfully with lactated Ringer's solution (pH adjusted to 8.2), while vaporizational heat losses have been controlled by one of three methods.

No significant sustained rise in venous pressure, and no pulmonary edema occurred in any

[7] Burns that heal in 21 days or less are not counted as recordable injury.

[8] Burned areas that heal within 21 days after the injury are excluded from these area estimates.

case, although the volumes of fluid given in most cases far exceeded all extant recommended amounts.

No renal insufficiency occurred, although a hemoglobinuria exceeding 500 mg.% existed during the first three hours of treatment in two cases.

No tracheostomy was needed or performed, although deep burns covered the faces and necks of 7 of the 10 cases.

Recovery from shock occurred during the intravenous infusion of lactated Ringer's solution in 6 of the 10 cases, while the hematocrits increased. This indicates that burn-shock is not primarily oligemic in origin, but is mainly relatable to the biologic action of extravascular sodium deficiency.

The colloid and blood needed for the successful treatment of shock associated with burns covering up to 85% of the body surface of human beings is zero. Whether any colloid or blood might be of value in the treatment of shock in cases of burns larger than 85% of body surface is as yet unknown.

What part, if any, the control of vaporizational heat losses played in the successes attained in the treatment of shock in these cases is indeterminate.

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The History and Significance of Serendipity in Medical Discovery[1]

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CONSIDERABLE literature exists regarding the methods which scientists follow in carrying on their research work. It appears that there is no one royal road to scientific discovery and that the personality and temperament of the individual scientist determine the actual work methods which he may follow. However, there are some broad patterns which may be discerned. The purpose of this paper is to explore the role of serendipity in medical discoveries and to relate some of the dramatic accounts of lucky accidents.

In 1754 Horace Walpole coined the word "serendipity" based upon his reading of a fairy tale entitled "The Three Princes of Serendip" (38). "As their highnesses traveled," wrote Walpole, "they were always making discoveries by accident or sagacity, of things which they were not in quest of" (6). Thus, serendipity may be defined as "the happy faculty, or luck of finding unforeseen evidence of one's ideas or, with surprise, coming upon new objects or relations which were not being sought" (6).

In popular usage the phrase accidental discovery is often substituted for the word serendipity. Unfortunately, it connotes a chance occurrence which entails no thought on the part of the scientist and which arises like Athena, who sprang full-grown from the head of Zeus. However, the numerous examples cited in this essay attest to the fact that serendipity is the product of the proper environment *and* an inquiring mind. In the words of Pasteur, "In the field of observation chance favors only the prepared mind." Joseph Henry stated, "The seeds of great discoveries are constantly floating around us, but they only take root in minds well prepared to receive them" (7). In other words, chance merely provides the opportunity, while the scientist must recognize and comprehend its significance.

The oft-quoted discovery of penicillin by Sir Alexander Fleming is an illustration of this principle. In 1929 Fleming noticed that one of his cultures of staphylococci had become accidentally contaminated by the green mold *Penicillium notatum*, and that for some distance around the mold growth the staphylococcal colonies were undergoing dissolution. Fleming later described his discovery as follows:

> "When I first noticed the action of penicillin, I was playing with a culture of staphylococcus, doing nothing very important. Actually, what had happened was that I had contracted to write the chapter of a book on staphylococcus. A man had written saying that by certain methods he could make the colonies of staphylococcus appear not a bit like themselves. I was trying to see whether he was telling the truth. I had some culture plates of staphylococcus, looked at them occasionally under a microscope, put the cover back on and set them aside for a while. When some people have finished with a culture plate they throw it aside, and that is the end of it. They miss a lot of peculiar things that happen by accident. I didn't throw those plates away, and later on they became contaminated. Of course, if you take off the cover of a culture plate things get in from the air. One of these plates got contaminated with a mold. That wasn't unusual. We had often had plates contaminated with molds before and hadn't paid much attention to them, except to use appropriate language and throw them away. But this time there was something different on the plate. The mold itself wasn't a bit unusual. The microbes in the neighborhood of that mold colony seemed to be dissolving. That was

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worth paying attention to. At least I thought it was, and I didn't pursue the original staphylococcal research. I touched that mold with a platinum wire and transferred some of the spores to another tube, off by themselves; there we had a pure culture of the mold that we could keep and experiment with. I knew nothing at all about molds at that stage of the proceedings. A mold starts off with a little spore, a tiny thing, smaller than a red blood corpuscle. When it grows it sends out a sprout or two, which branch again and again to produce the mass of mold that you recognize on bread, or cheese, for example.

"We then tried to see what this mold did. One of the first steps, an easy one, was to put it on another culture plate. You take a fresh culture plate, plant the mold and let it grow in the room. You don't want an incubator for this; an ordinary room will do beautifully for mold. Just let it grow for three or four days. Next we took different microbes, whichever were handy, and streaked them across the plate up to the mold. Some of them grew right up to the mold; some of them didn't go anywhere near it. So here we had a mold that made something which diffused out into the agar and stopped the growth of some of the microbes, but not of others" (33).

Fleming was not the first to observe the inhibition of staphylococcal colonies by molds. In 1876 an English physicist named John Tyndall experienced a similar fortuity, but failed to comprehend its full significance and attributed the bacterial death to asphyxiation (40). In the early 1900's Professor M'Fadyean of the Royal Veterinary College made the following remarks to his students:

"Look at this as a warning against delay. I inoculated this medium with a loop of material containing staphylococci, but before I could place the cover over the Petri dish a spore of some kind of fungus floating about in the air alighted upon the culture medium. It will be noticed that while some of the colonies of staphylococci have grown prolifically, the growth from this spore of a parasitic fungus, apparently akin to the ordinary common mould, has also flourished, and it will be further noticed that the growth of this fungus has had a very marked deleterious action on the growth of the staphylococci, either owing to the exhalation of something, or the addition of something to the culture medium, which has been decidedly inimical to the colonies of staphylococci. In fact the growth of colonies immediately adjacent to the fungoid growth appears to have been completely inhibited. The only thing to do now is to throw the culture away" (26).

M'Fadyean's concluding sentence is especially noteworthy. Although Tyndall, M'Fadyean, and even Pasteur had observed the phenomenon of microbial antagonism before Fleming, they all failed to perceive its significance or to investigate the phenomenon further. In contrast, Fleming "didn't pursue the original staphylococcal research" but went on "to see what this mold did" (33). Fleming has stated, "I had no suspicion that I got a clue to the most powerful therapeutic substance yet used to defeat bacterial infections in the human body. But the appearance of that culture plate was such that I thought it should not be neglected" (41). Therefore, instead of discarding the culture, Fleming isolated the mold, made an extract, and found it was bactericidal, and nontoxic when injected into animals. He even tried it in a local dressing for septic wounds. The clinical results were not impressive because of the low potency and instability of the crude material (17). Fleming was also unsuccessful in isolating the active principle in pure form. Fleming's work remained dormant for eleven years until Florey and Chain successfully extracted the antibiotic.

Prior to his discovery of penicillin, Fleming had discovered in 1921 another antibacterial agent, lysozyme—a component of nasal mucus, tears and egg white—which destroyed bacterial colonies on the surface of an agar plate. He subsequently persisted in his search for an effective bactericidal agent, and possessed with the experience of lysozyme he quickly saw the possibilities of the activity of the mold. Fleming, himself, stated, "It was fortunate that . . . I was always on the lookout for new bacterial inhibitors, and when I noticed on a culture plate that the staphylococcal colonies in the neighborhood of the mold had faded away, I was sufficiently interested in the antibacterial substance produced by the mold to pursue the subject" (41). Thus, Fleming's mind was "prepared" for serendipity not only as a result of his curiosity and insight, but also because of his background of knowledge accumulated by years of work which enabled him to make pertinent mental associations.

There are many examples of "lost serendipity" or discoveries which were overlooked because of a lack of astute observation on the part of an investigator. W. H. George has said that "What is observed depends on who is looking" (15). True observation is dependent upon a mental as well as a sensory process (4).

Roentgen's discovery of x-rays was fortuitous. Working in a darkened laboratory in 1895 with a cathode ray tube enclosed in a black paper jacket, Roentgen was attempting to detect invisible rays on a barium platinocyanide screen, but did not expect such rays to penetrate opaque materials. By chance he noticed that the barium platinocyanide screen on the bench near his vacuum tube became fluorescent although it was separated from the tube by black paper. He also noticed that when his hand passed between the tube and the screen, a faint image of the bones of his hand appeared on the screen. He went on to show that the radiolucency of objects varies with their thickness and density, thus paving the way for diagnostic radiology.

Many other physicists had found that their photographic plates were fogged when kept near a cathode ray tube, but only Roentgen noticed the cause as a result of his astute observation. Lord Rayleigh relates:

> "It was a source of great annoyance to Crookes that he missed the discovery of the x-rays. According to the account he gave in my hearing, he had definitely found previously unopened boxes of plates in his laboratory to be fogged for no assignable reason and, acting I suppose in accordance with the usual human instinct of blaming someone else when things go wrong, he complained to the makers [of the plates], who naturally had no satisfactory explanation to offer. I believe it was only after Roentgen's discovery that he connected this with the use of highly exhausted vacuum tubes in the neighborhood" (7).

Another English scientist also observed that cathode ray tubes fogged nearby photographic plates, but concluded only that such plates should always be stored elsewhere (7)! This train of thought is similar to that of M'Fadyean's with respect to contaminated staphylococci cultures: "The only thing to do now is to throw the culture away." Such reactions typify scientists who have made significant observations, but have failed to ask the question "Why?" or to make an effort to follow up their puzzling observations.

Another interesting case of lost serendipity is related by J. T. Edwards:

> "On the particular occasion under recall, I had inoculated a very large number of Roux flasks to obtain antigen, and was struck with the greatly increased growth over the whole agar surface in one of these flasks. All that seemed to account for the difference was a semicircular patch, over an inch and a half in radius, ingrowing into the culture medium at the very mouth of the flask, of a dry looking, wrinkled, very slowly spreading, somewhat brownish or greyish brown mould. On withdrawing the plug, there escaped a very pungent mouldy odour.
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> "Believing then I was on the scent of a possibly important finding I took the flasks over from the old 'Physics Lab.,' where they had been incubated, across the quadrangle of the College to the 'Main Lab.' to show them at once to M'Fadyean. In company with the genial Captain Metivier, who had just joined us on release from the Army and also, I strongly believe, the pensive Mr. Rucker, of Chile, who had been with us much longer, I awaited the coming of the great man down the stairs from the old converted farrier's quarters above where he had been dictating the morning's letters to his typist.
>
> "At last, he came slowly down and, enthusiastically, I recounted to him what I had seen. Coming to the point in my narrative where I said that I noticed the mould gave off a stink, he broke silence, saying, coldly, '*H'm—even a oacillus cannot live on a stink!*': and he walked on. Metivier rocked with laughter at the characteristically withering observation.
>
> "Shortly afterwards it was left, *for others*, to place on record one important property of the organism that has since come to be known as *Brucella abortus*, namely, its CO_2 requirements, and these, we now know, would have been supplied in abundance, at any rate, by the stinking mould" (11)!

There are many other fascinating examples of lost serendipity in medical discoveries. Sir F. M. Burnet observed the agglutination of chick embryo erythrocytes in the presence of influenza virus, but failed to follow it up. Later, in 1941, George Hirst was working with chick embryos infected with influenza virus in an attempt to produce a vaccine. "When the allantoic fluid from chick embryos previously infected with strains of influenza A virus was being removed, it was noted that

the red cells of the infected chick, coming from ruptured vessels, agglutinated in the allantoic fluid. Since red cells in the allantoic fluid of chick embryos inoculated with sterile materials did not agglutinate at all, it seemed that the agglutination phenomenon might be the result of infection with influenza virus in the chick" (22). Because this observation was not overlooked and was studied further, it furnished a method for the quantitation and identification of influenza virus, and led to the discovery of specific receptor sites on living cells for virus attachment.

In virtually all accidental discoveries, the significant factor has been not so much the accident itself as its observation, comprehension and interpretation by the alert scientist. Furthermore, he should be engaged simultaneously on several aspects of the same problem and not disregard matters outside his principal objective. As a result, his mind will be prepared for the unexpected. Heraclitus has stated, "Unless you expect the unexpected you will never find [truth], for it is hard to discover and hard to attain."

The discovery of chromosome nondisjunction by C. B. Bridges is an admirable demonstration of the maxim "Treasure your exceptions." When a white-eyed female Drosophila is bred to a red-eyed male (the genes for eye color being sex-linked), all the daughters will be red-eyed heterozygotes and all the sons white-eyed. Bridges, however, discovered that very rarely (about once in three thousand), a white-eyed daughter and red-eyed son were produced. The first impulse of many investigators might be to discard the unexpected exception and attribute it to experimental error. Bridges, however, heeded the exceptional offspring and hypothesized that they could be explained by the failure of the two X chromosomes in the white-eyed mother to segregate during the first meiotic division. Bridges subsequently tested and confirmed his predictions by microscopic examination of the chromosomes of the exceptional offspring (44). Thus his alert observation and insight led to a proof of the chromosome theory of heredity.

The discovery by Barr and Bertram of sexual dimorphism in nuclear structure was also the result of investigation of an unexpected discovery. In 1949 these researchers were engaged in experiments on nerve fatigue, specifically on the electrical stimulation of the hypoglossal nerve of the cat. In the course of their histological studies they noted that a distinctive focal mass of nuclear chromatin was present in the cells of some cats, but was absent in others. Pursuit of this observation led to the conclusion that the nucleolar satellite was present in female cats, but not in males. It was found that the presence of "sex chromatin" provided a simple method for assessing chromosomal sex in other mammals including man. Reliable techniques have since been developed for detecting the sex chromatin pattern by using accessible tissues such as skin, buccal or vaginal mucosa, and leukocytes. Such techniques have been especially useful in pediatric diagnosis of abnormalities of sex differentiation (47).

The development of cholecystography by Graham and Cole is another dramatic example of a discovery which might not have been made had not the investigators pursued an exceptional unexpected finding. It is interesting that accident as well as hunch and design played a role in this discovery, which is recounted below by Dr. Graham:

"It is difficult to recall exactly how the idea of the possibility of visualizing the gall bladder by the use of phenolphthalein derivatives presented itself. . . . the late Walter Mills and I had spoken of the desirability of visualizing the gall bladder in some manner comparable to the visualization of the stomach and other parts of the alimentary canal. No satisfactory method, however, suggested itself until suddenly one evening, in the winter of 1922, the idea occurred to me that since Abel and Rowntree had demonstrated the fact that the chlorinated phenolphthaleins are excreted almost entirely through the bile it might be possible, by substituting for the chlorine atoms other atoms which would be opaque to the x-ray, to obtain a shadow of the gall bladder.

". . . I was able to obtain some of the free acid of tetraiodophenolphthalein from the Eastman Kodak

Co. This was advertised in a list of various indicators. After receiving the material I turned it over to Warren Cole, in July, 1923, and asked him to inject it into some animals to see if he could visualize their gall bladders with it . . . Before injecting the material into dogs we converted it into the sodium salt because the free acid was naturally less soluble than the sodium salt. Six dogs were injected intravenously, and x-ray photographs were made of the gall bladder regions in all of them at frequent intervals after the injection. In five of the dogs no shadow was obtained, but fortunately a faint shadow was obtained in the sixth one. At first we were at a loss to understand why we had obtained a faint shadow in one dog but none at all in the other five animals. The idea then occurred to us that the reason for the failure was probably due to the fact that the animals were not fasting and that, therefore, the injected substance was not staying in the gall bladder for a long enough time to be concentrated and, therefore, to make a shadow. From the standpoint of the future development of cholecystography we often feel grateful to that one dog which cast a shadow, probably because he was accidentally given no food. If we had failed to get a shadow in all of these animals we probably should have abandoned the whole idea as a fruitless one. It is curious on how fragile a thread the destiny of some events hang. When we came to investigate the matter we found that, as a matter of fact, through some mishap the animal keeper during the time of the experiment had for some reason neglected to feed the one dog on the morning of the injection but he had fed all the others. Greater efficiency on the part of the animal keeper would doubtless have resulted in a complete failure of our experiment and, therefore, we would have given up the whole idea. Sometimes efficiency can be a curse" (19).

There are many examples of serendipity in microbiology which might have been missed had not the investigator been motivated by intellectual curiosity. Pasteur discovered immunization by chance. During the years 1880–1882 he had been studying chicken cholera and one day he happened to inoculate some laboratory hens with an old culture rather than the usual fresh one. To his surprise, he noticed that they became ill and then recovered, but did not die as expected. At a later date he re-inoculated them with a fresh culture, along with other chickens. He observed that only the chickens which had previously been inoculated with the old cultures survived subsequent exposure to the virulent cholera. Pasteur realized the significance of the accident was that attenuated cultures somehow provide protection against further infection. He also had the insight to appreciate the potentiality and applicability of his discovery: "This is my most remarkable discovery," he said, "a vaccine more scientific than the one for smallpox where no one has seen the germ; we will apply this to anthrax and we will save lives" (33).

The discovery of anaphylaxis by Charles Richet was due to an accidental observation. Richet was investigating the toxic dose of an extract prepared from the sea anemone upon laboratory animals. While attempting to immunize animals which had survived the toxic dose, he found that a much smaller second dose, given some time after the first, was promptly fatal. Richet was astonished with his discovery. He found it difficult to believe that the result was due to anything he had done and testified that he had discovered "induced sensitization" in spite of himself (7)!

The Schultz-Dale phenomenon, another manifestation of anaphylaxis, was discovered accidentally by Sir Henry Dale. While applying horse serum to strips of involuntary muscle taken from guinea-pigs, he encountered one strip which responded with a violent contraction after application of a trace of horse serum. Dale describes his own response as follows:

"And it occurred to me that many guinea pigs in that laboratory were used for testing the strength of antitoxic horse serum, and that an economically minded colleague might have provided me with a survivor from such a test. The verification of that suspicion gave us a new idea about the meaning of the anaphylactic or allergic condition; but it took many years more, and a great deal of work in many laboratories in different countries, before we were able to establish the fact that histamine is a natural constituent of most cells of the living body which is normally held harmless and inactive in their interior but is released, so as to produce its characteristic effects, if the living cells come into contact with some substance from a plant or animal—grass pollen, scurf from a skin, and so forth—to which they have become abnormally sensitive or allergic" (9).

The concluding remarks of Dale demonstrate that although many outstanding medical discoveries have arisen as fortuitous occurrences, dependent upon close observation, curiosity, and insight, their complete elucidation has necessitated many years of subsequent painstaking research, based on design rather than chance. Such was also the case with penicillin, the commercialization of which required many years of long, arduous work by Florey, Chain and others after the initial discovery by Fleming.

The Weil-Felix reaction—a serologic test commonly used in the diagnosis of rickettsial diseases—was the outcome of a chance event. In 1915 Weil and Felix were investigating cases of louse-borne typhus in Poland and isolated the bacterium known as Proteus X from some patients. Because they believed that it might be the cause of the disease, they tried agglutination of the organism with the patients' sera and obtained positive results. Although it was subsequently shown that Proteus X does not cause the disease, agglutination of this organism proved to be a reliable and valuable means of diagnosing typhus (4). It is now known that patients with rickettsial infections develop antibodies which agglutinate certain strains of Proteus vulgaris because rickettsial and Proteus organisms share certain antigens in common.

The Danish physician, Christian Gram, in 1884 accidentally discovered the bacterial stain named after him when trying to develop a double stain for kidney sections. Hoping to dye the tubular nuclei violet and the cytoplasm brown, he used gentian violet followed by Lugol's solution. Instead of the intended result, however, Gram found that the application of iodine facilitated destaining of the tissue by a subsequent alcohol step. During this work, Gram observed that certain kinds of bacteria resisted decolorization and remained blue-black, whereas others were decolorized and took only the counterstain. However, he failed to realize the value of the stain in differentiation (51).

The acid-fast method of staining tubercle bacilli was discovered accidentally by Paul Ehrlich when he inadvertently left some slide preparations on a hot stove. The heat was the necessary factor in making the bacilli take the stain. Robert Koch said, "We owe it to this circumstance alone that it has become a general custom to search for the bacillus in sputum" (4).

Perhaps the most numerous as well as the most striking examples of serendipity are found in the field of chemotherapy. Penicillin has already been mentioned. The discovery of the sulfonamides is another example. Ehrlich had believed that since some dyes selectively stained micro-organisms, it might be possible to find a chemotherapeutic agent which was selectively toxic as a result of selective fixation to the infective agent. In his search Erhlich had no success until he tested his six hundred and sixth compound, salvarsan, an arsenical compound which was effective against syphilis. Such success was the result of trial-and-error investigation and involved no element of chance. Gerhard Domagk, however, carried on Ehrlich's search and tested a great number of azo dyes. In 1932 he found an azo dye, prontosil, which was effective therapeutically against streptococci. Ironically, it was later found that the active principle of prontosil was sulfanilamide, which is not a dye! Thus this discovery was "accidental" in the true sense of the word. The "prepared mind" was primed with Ehrlich's false hypothesis!

Another interesting outgrowth of Ehrlich's attempt to find a compound for the treatment of syphilis was the discovery of organic mercurial diuretics in 1919. This resulted when a diligent nurse observed the potent diuretic properties of a weak antisyphilitic agent, novasurol, which was administered to a patient with congenital syphilis (50).

The discovery of long-acting depot penicillin is allegedly an accidental one. It resulted when a physician decided to mix procaine and penicillin within the syringe in order to obviate an initial procaine injection which he

used to lessen the pain of penicillin injection (21).

Beveridge recounts an accidental discovery of a more effective means of administration of sulfapyridine:

> "Sir Lionel Whitby . . . was conducting an experiment on the then new drug, sulphapyridine, and mice inoculated with pneumococci were being dosed throughout the day, but were not treated during the night. Sir Lionel had been out to a dinner party and before returning home visited the laboratory to see how the mice were getting on, and while there light-heartedly gave the mice a further dose of the drug. These mice resisted the pneumococci better than any mice had ever done before. Not till about a week later did Sir Lionel realize that it was the extra dose at midnight which had been responsible for the excellent results. From that time, both mice and man were dosed day and night when under sulphonamide treatment and they benefited much more than under the old routine" (4).

Many of the drug sources known in ancient times were apparently discovered by accident. For example, according to an old South American Indian legend, the curative power of cinchona bark (containing quinine) for malaria was discovered by a sick feverish Indian lost in the jungle. He quenched his thirst by drinking from a pool of water. From the bitter taste of the water, he recognized that it was tainted with the poison from the quina-quina tree. Although he shared this fictitious belief, he drank deeply so as to bring about a quick death. To his great surprise, he recovered completely. When he returned to his village, he told the story of his cure and thereafter cinchona bark was used as a medicine for the fever prevalent in that region. The Incas later taught the Spanish conquistadors that malaria could be cured with cinchona extract (41).

It is interesting to note that in 1856 William Perkin, while attempting to synthesize quinine, accidentally produced the first synthetic aniline dye.

Daraprim is a drug that was designed as an antipyrimidine. However, when tested on lactobacilli it proved to be an antifolic. It was also shown to be an antimalarial. Today it is used in South America as an adjunct to table salt for the chemoprophylaxis of malaria.

Many cathartics have been discovered by accident. Epsom salts (magnesium sulfate) were discovered in 1618 when a farmer found that his oxen would not drink at a spring in Epsom Downs. The farmer tasted the water, found that it was bitter, and told the local townspeople of his discovery. They began to use the water externally for cutaneous sores. A nobleman, Lord Dudley North, was the first to use it internally and demonstrated its cathartic properties. Subsequently, society flocked to Epsom to partake of the waters!

Several of the vitamins and related drugs were discovered as a result of serendipity. In 1929 Henrik Dam, a Danish biochemist, was experimenting with chickens to determine whether they could synthesize cholesterol. He happened to notice extensive spontaneous hemorrhages when the chickens were fed a special restricted synthetic diet. Clotting time was also prolonged in these animals. Dam continued to work on the problem for a number of years and in 1935 reported that the hemorrhagic diathesis was due to a deficiency of an unidentified fat-soluble dietary factor which he named vitamin K ("Koagulation" vitamin) (33). It was later shown by other workers that vitamin K promotes prothrombin formation in the liver.

The discovery of the anticoagulant Dicumarol (bishydroxycoumarin) was the outgrowth of an investigation of "sweet clover disease" in cattle. In the winter of 1921–1922, veterinarians in Alberta, Canada, and in North Dakota reported a new disease in cattle characterized by excessive and sometimes fatal bleeding. Further study of the disease revealed that the bleeding was due to a prothrombin deficiency caused by a poison in spoiled sweet clover hay. The causative agent was finally isolated in pure crystalline form by Campbell and Link in 1941 (25). Today coumarin derivatives are extensively used as anticoagulants in medicine and surgery.

Christian Eijkman, a Dutch physician in Java, discovered the cause of beri-beri through

a fortunate circumstance. When the stock of chicken feed for his laboratory chickens was depleted, he fed them on table scraps from the hospital, which consisted mainly of polished rice. The chickens subsequently developed beri-beri. Eijkman found that the chickens were cured when rice polishings were added to the diet. Similar results were obtained when the observations were transferred to man. Some time later, in 1913, Funk isolated from rice polishings a crystalline substance (vitamin B) which was effective in the prevention and the cure of experimental beriberi (5).

A great number of relatively new drugs have been the result of accidental discoveries made by experimenters seeking solutions to particular problems. However, in these cases, unexpected events led to the discovery of something of an entirely different nature, for which the experimenter was not looking.

In 1954, H. Franke was testing the effectiveness of a new sulfonamide, carbutamide, in cases of pneumonia and happened to notice symptoms resembling those of hyperinsulinism. The action of the drug was confirmed by J. Fuchs by trial on diabetic patients. Thus, the accidental discovery of the hypoglycemic action of carbutamide initiated the use of "oral hypoglycemic agents" (3).

The sweetening power of saccharin was accidentally discovered by C. Fahlberg in 1879 in the course of an investigation on the oxidation of o-toluene-sulfonamide. Fahlberg happened to eat lunch without washing his hands after performing some experiments. A chemical on his fingers gave his sandwich an unusually sweet taste. He returned to the laboratory and tested the contents of each beaker until he found the product responsible.

The hallucinogenic properties of lysergic acid diethylamide (LSD) were accidentally discovered and described in 1943 by Albert Hofmann, a Swiss chemist. While working with the chemical in his laboratory one day, he experienced a peculiar restlessness associated with slight dizziness. Fantastic images of extraordinary plasticity and vivid kaleidoscopic coloring passed through his mind. He had to interrupt his work and go home to rest. While at home, he conscientiously recorded every sensation he experienced. He later attributed his disturbance to the chemical he had been preparing (39). As a result of further experiments, Hofmann's observations were fully confirmed by others. LSD has since proven to be a valuable experimental tool for the study of psychoses, especially schizophrenia which it may simulate. In fact, it has been proposed that LSD exerts its mental effects by interference with serotonin and that schizophrenia may therefore be due to abnormal serotonin metabolism. LSD may also prove to be useful as an adjunct to psychotherapy.

The sensitizing effect of Antabuse (tetraethylthiuramdisulfide or TETD) to ethyl alcohol was discovered accidentally by Hald and Jacobsen. This compound had been used in the rubber industry as an anti-oxidant. "Although workers exposed to it develop hypersensitivity to ethyl alcohol, no published report on the subject appeared until two Danish physicians, who had taken TETD in the course of an investigation of its potential anthelminthic usefulness, became ill at a cocktail party. Quick to realize that the TETD had altered their response to alcohol, they then initiated a series of pharmacological and clinical studies which provided the basis for the use of TETD as an adjunct in the treatment of chronic alcoholism" (20).

Benzedrine (amphetamine) was originally developed by Smith, Kline & French Laboratories as a nasal decongestant. However, it had some disturbing side effects: central nervous system stimulation and anorexia. Nevertheless, someone with insight suggested that these side effects might be profitable, and that the drug might have some psychiatric use. This was found to be the case, and today Benzedrine is used therapeutically for the treatment of mild depression or overweight (49).

Isoniazid, one of the most effective drugs for the chemotherapy of tuberculosis, was

discovered accidentally. In 1945 Chorine reported that nicotinamide was tuberculostatic. Further studies of the structure-activity relationship of related compounds revealed that isonicotinic acid derivatives possessed tuberculostatic activity. Since thiosemicarbazones were also known to be tuberculostatic, an attempt was made to synthesize and study the thiosemicarbazone of isonicotinic acid. Although the thiosemicarbazide, which was the objective of the synthesis, did not possess outstanding activity, the intermediary, isoniazid, was found to be more potent as a tuberculostatic agent than any known substance, synthetic or antibiotic (17).

Iproniazid, a congener of Isoniazid, was also discovered fortuitously. When it was first used for the treatment of tuberculosis it was noted to produce an elevation in mood and euphoria in some of the patients (36). At a later date it was shown to act as a monoamine oxidase inhibitor, possibly accounting for its central antidepressant action. Although its use has been limited by the frequency of hepatotoxicity, it is recognized as the first potent compound of its class to be used extensively in psychiatry.

Chlorpromazine (Thorazine) was first introduced into therapeutic practice in anesthesiology where it was used to potentiate and prolong the action of anesthetics, sedatives and narcotics. In France, chlorpromazine was used as an ingredient of the "lytic cocktail" (chlorpromazine, meperidine, and promethazine) which was proposed by Laborit as an advanced anesthetic supplement for difficult surgery (10). It was the subsequent observation, in surgical patients treated with chlorpromazine, of a peculiar detachment from the environment without other marked mental changes, that led to its introduction in psychiatric therapy (28). Chlorpromazine is now widely used psychiatrically as a tranquilizer to dispel anxiety, delusions or hallucinations without clouding consciousness or dulling mental faculties.

The effectiveness of Dramamine in the prophylaxis and treatment of motion sickness was discovered by chance in 1947 when the drug was sent by Searle & Co. to The Johns Hopkins University Allergy Clinic for experimental investigation of its possible value in the control of hayfever and urticaria. One of the patients who received the drug was a pregnant woman with urticaria who incidentally had suffered all her life from car sickness. It was observed that she experienced no unpleasant sensations provided the drug was taken just before travel. A placebo failed repeatedly. It was subsequently shown that other victims of car sickness and airsickness were, without exception, also freed of discomfort as a result of Dramamine (14).

The cranberry crisis in November 1959 may have yielded an unexpected benefit. The herbicide, aminotriazole, was found to be a trace contaminant in some batches of cranberries. The implication of this compound as a carcinogen prompted withdrawal of all cranberries from the market. However, it was found that the alleged carcinogenic activity was due to its antithyroid effect. Dr. E. B. Astwood, a professor at Tufts Medical School, wrote:

> "Before the cranberry episode my associates and I had been looking for an antithyroid compound that might have a longer duration of action than those currently in use for the treatment of hyperthyroidism and Dr. W. E. Mayberry had found that aminotriazole might be such a compound. A single oral dose of 100 mg. inhibited radioiodine uptake by the thyroid of normal and thyrotoxic subjects for 24 hours, which means that there is a possibility of therapy with one dose per day; 10 mg. had only a slight effect. Should experience show the compound to be well tolerated, we will be faced with the anomalous situation that an effective remedy suitable for human use is banned from use in killing weeds" (1).

The examples of serendipity in the field of chemotherapy cited above thus demonstrate that experiments designed to find solutions to particular problems may often yield negative results with respect to those problems. However, in the process, the investigator may perceive a clue which throws light on an entirely different problem, thereby stimulating a new line of research. Unless he

abandons his original problem and follows the new clue, he may miss an important discovery. In this connection Claude Bernard stated, "We must never be too absorbed by the thought we are pursuing" (4).

Bernard's recognition of the significance of chance phenomena unrelated to his initial experimental plan led to his discovery of the action of pancreatic juice, the function of the vasomotor nerves, and the glycogenic function of the liver. Goldstein relates the following account in the *Annals of Medical History*:

> "Practically all of the present-day knowledge of absorption of food materials was determined in the light of Bernard's discoveries relating to intestinal digestion. . . . It was the picture of fat emulsification that first brought his attention to pancreatic secretion. He was investigating comparative digestion in herbivorous and carnivorous animals and noted that fat introduced into the stomach of a rabbit did not become milky and chyle-like until it reached a point much lower in the intestine than was observed when a similar procedure was instituted in a dog . . . , where the entrance of the pancreatic duct is common with the bile duct. He further noticed that fat emulsification always occurs below the entrance of the pancreatic duct and never above it, thus excluding the action of the bile. He immediately discontinued his study, investigated the nature of this phenomenon, which culminated in the discovery of the digestive nature of the pancreatic secretion" (16).

Bernard's discovery of the vasomotor nerves established the reflex control of the circulation. Bernard hypothesized that impulses passing along nerve fibers set up chemical changes producing heat. In order to test his theory he measured the temperature of a rabbit's ear and then severed the cervical sympathetic nerve on that side, expecting that the ear would become cooler than its opposite. To his great surprise it became warmer. Bernard abandoned his original hypothesis and accepted the new observed fact. Brown-Séquard later demonstrated that the increased temperature was due to a release from the neurogenic control which normally produces vasoconstriction.

The glycogenic function of the liver was also discovered by Bernard. While assaying carbohydrate content of livers of animals in different physiologic circumstances, he happened to postpone one analysis until a day after the animal's death. Bernard found a larger amount of sugar than expected in this determination, a fact which led to his discovery that sugar had a precursor in the liver which he called glycogen (37). Bernard stated:

> "We must never neglect anything in our observation of fact, and I consider it indispensable, never to admit the existence of an unproved source of error in an experiment and always to try to find a reason for the abnormal circumstances that we observe. Nothing is accidental, and what seems to us accident is only an unknown fact whose explanation may furnish the occasion for a more or less important discovery. So it proved in this case" (37).

Many fundamental discoveries in physiology were the result of serendipity. One of the earliest was the origin of electrophysiology. When the wife of Luigi Galvani became ill in 1780 in the city of Bologna, a diet of frogs' legs was prescribed for her. The frogs' legs, which were suspended by copper wire from an iron balustrade, were observed to twitch when blown by the wind against the iron (6). This observation led to many important experiments, including those of Volta on the production of electrical currents by contact of two dissimilar metals and thus to the invention of the electric battery. It also led to the work of Du Bois-Reymond, who first demonstrated the action potential of nerve in 1843.

The discovery of the relationship of diabetes to pancreatic disease was due to a chance observation. In the 1880's von Mering and Minkowski were studying the role of the pancreas in digestion, and performed pancreatectomy in a number of dogs. A laboratory assistant happened to notice that swarms of flies were attracted to the urine of these animals and mentioned this to the investigators. Analysis of the urine revealed substantial glycosuria. Thus for the first time experimental diabetes was produced.

Dr. Walter Cannon's extensive research on the physiologic effects of fear and rage was initiated by an unexpected finding. While

radiographically studying the movements of the barium-filled intestinal tract, Cannon unexpectedly observed that anxiety results in a cessation of gastrointestinal motility (5).

It may appear surprising that Ringer's solution, composed of dissolved salts in carefully adjusted proportions, was the consequence of an error made by a careless laboratory technician. Dr. Sidney Ringer, a physician at the London University College Hospital, had found that an isotonic solution of pure sodium chloride maintained the beat of isolated frogs' hearts for only a short time. However, on one occasion he was surprised and puzzled to find that his frogs' hearts continued to beat for many hours. First believing this was a seasonal effect, he later found that his laboratory assistant had used tap water instead of distilled water to prepare the saline solution. The small proportion of calcium ions in the tap water was effective in making a physiologically balanced solution. As a result of further analysis, a small proportion of a potassium salt was also added, and Ringer's solution was complete (9). Today this solution is used in a great number of medical and biological research procedures.

There are many examples of accidental discoveries which might have been disregarded had not the investigator realized their potentiality and applicability. In these cases mere observation on the part of the physician was insufficient to actualize the discovery; opportunism was also an indispensable factor. Pasteur's awareness of the practical aspects of immunization has already been mentioned. Another instance of such insight was the discovery by Dr. William G. Spiller of cordotomy for the relief of intractable pain. This followed his observation of a hospitalized patient who had lost pain and temperature sensation up to a level on his trunk, without paralysis. When this patient died from tuberculosis, a post-mortem examination revealed two small tuberculous nodules in the spinothalamic tracts of his spinal cord. "Spiller at once saw the possibility of turning the misfortune of his patient to the good of others. He persuaded a surgeon, Martin, to divide this part of the spinal cord in another person with unbearable pain. The result was so great a success that the operation has since become a standard one" (24).

The element of opportunism in serendipity was also a major factor in the discovery of spinal anesthesia in 1885 by J. Leonard Corning, a New York neurologist. Corning was investigating the action of cocaine on the spinal nerves of dogs, and hoped that injected cocaine might travel along the spinal nerves so as to affect the cord itself. On one occasion he accidentally pierced the dura and his injection produced spinal anesthesia, with transient paralysis of the dog's hind legs. Corning recognized the applicability of his discovery and, after successful trials on patients, suggested its possible use in surgical practice (29).

Although the gastric fistula of Alexis St. Martin was not the first recorded case, Dr. William Beaumont was the first to recognize opportunity in this historic accident and so became a pioneer in gastric physiology (30). Sir Arthur Hurst has described the circumstances of this investigation:

"In the early 1820's Alexis St. Martin, a young Canadian trapper, received a gunshot wound in the abdomen. He came under the care of William Beaumont, a surgeon in the United States Army, who took him into his own house and for two years nursed him back to health. The wound eventually healed, leaving a gastric fistula surrounded by a ring of prolapsed mucous membrane. Beaumont, who was endowed with the same spirit of enquiry as Harvey, engaged St. Martin as his servant, and for two periods between 1825 and 1833, amounting in all to twenty-four months, made almost daily observations and experiments, which laid the foundation of our knowledge of gastric digestion. Harvey's observations were concerned with the mechanical action of the stomach in altering the physical properties of the food so as to render it fit for absorption. Beaumont's work was concerned with the changes which occur in the stomach as a result of the digestive activity of the gastric juice. He described the physical properties of gastric juice and had samples analysed, confirming Prout's recent discovery that it contained free hydrochloric acid. He showed that the juice is secreted only in response to the entry of food into the stomach and demonstrated its action on different kinds of food both within the body and *in vitro*. He recorded

how, as a result of fear and anger, febrile disturbances, and excessive indulgence in alcohol the gastric mucous membrane became red and swollen and the juice was replaced by a secretion of mucus" (22).

The development of collateral circulation was not only discovered accidentally by John Hunter, but also employed by him to the advantage of a patient. Once in Richmond Park he ligated one external carotid artery of a deer. Although the antler on that side became cold to the touch, when he re-examined it a week later he was startled to find that it had regained its former warmth as well as growth. After sacrificing the buck he noticed that the ligated segment was circumvented by enlarged branches of the artery above and below the ligature. Hunter reasoned that regional circulation had been restored as a result of anastomosing branches. He concluded, "I must remember that." Some time later when he was called upon to treat a patient with a popliteal aneurysm, he chose not to amputate, as was customarily done, but, recalling his experience with the buck, he ligated the artery above the aneurysm. In six weeks the patient was discharged as well (33). To this date, the adductor canal of the thigh is eponymized with Hunter's name.

Serendipity and opportunism both played a role in the discovery of pneumoventriculography. Dr. Walter E. Dandy, a resident surgeon at Johns Hopkins in 1917, was consulted about a patient on the medical wards who was suspected of having an intestinal perforation with peritonitis. Although typhoid fever was thought to be the most likely diagnosis, acute miliary tuberculosis with intestinal involvement could not be ruled out and so a chest x-ray was made. This x-ray, which included the upper part of the abdomen, revealed sub-diaphragmatic air. An exploratory operation disclosed a perforation of the transverse colon due to typhoid fever. The observation of sub-diaphragmatic air was so striking to Dandy that it was instrumental in suggesting the injection of air into the cerebral ventricles or "pneumoventriculography" (5).

A great number of achievements in surgery have been due to a realization by the surgeon that a new, accidentally discovered technique might be applicable to an entirely different situation. One such example is the origin of the use of rubber gloves in the operating room. In 1889–90 the nurse in charge of Dr. William Halsted's operating room complained of a dermatitis due to the frequent immersion of her hands in the antiseptic fluids, carbolic acid and mercuric bichloride. In consequence Halsted requested the Goodyear Rubber Company to make an experimental pair of thin rubber gloves with gauntlets. These proved to be so satisfactory that additional gloves were ordered and these were adopted by other members of the surgical team. The value of the use of rubber gloves in the prevention of infections was appreciated some time after this.

The effectiveness of simple dressings for wounds was discovered accidentally on the battlefield by Ambroise Paré, a sixteenth century surgeon, when the supply of boiling oil for cauterization was depleted and he was forced to "apply in its place a digestive made of yolks of eggs, oil of roses, and turpentine" (33).

The surgical treatment of coarctation of the aorta by resection and end-to-end anastomosis was the outcome of an accidental experience of Crafoord. "In the course of operating on a patient with patent ductus arteriosus he found it necessary to occlude the aorta just below the left subclavian artery for 27 minutes in order to control bleeding and to close the aortic end of the ductus. The patient made a satisfactory recovery. Crafoord and Nylin reasoned that patients with coarctation, with their well-developed collateral arteries, should be able to tolerate occlusion for longer than 27 minutes" (5).

The first successful pneumonectomy for bronchial carcinoma was performed by Evarts Graham in 1933 when, upon starting to do a lobectomy on a forty-eight year old physician, he was unable to find a satisfactory interlobar fissure (45).

The Ramsted operation for congenital

hypertrophic pyloric stenosis was the outcome of chance. In 1911, Conrad Ramsted, when attempting a classical Fredet-Weber operation, had difficulty in closing the longitudinal incision by transverse suture because the tension of the wound edges was very great. He therefore left the mucosa exposed and covered it with a tag of omentum. This variant of the original procedure proved to be a great advance (33).

The surgical treatment of parkinsonism by means of occlusion of the anterior choroidal artery was discovered by Cooper as a result of an unintentional surgical accident during the execution of another operation for the relief of the same disorder.

> "In October 1952, during a craniotomy originally planned as a [left cerebral] pedunculotomy in a 39 year old man incapacitated by right-sided tremor and rigidity, the left anterior choroidal artery was [inadvertently] torn and had to be completely occluded [by applying silver clips]. Because of uncertainty as to the possible sequelae of occlusion of this vessel, the operation was terminated without cutting the peduncle. The postoperative course was notable for virtual disappearance of tremor and rigidity from the right extremities, without any lessening of motor power in these extremities.
>
> "During the postoperative observation of this patient, one could not suppress the speculation that the unplanned arterial occlusion had contributed to the alleviation of tremor and rigidity in this case" (8).

Cooper's speculation was subsequently confirmed. The experience with surgical occlusion of the anterior choroidal artery demonstrated conclusively that the incapacitation of parkinsonism is potentially reversible by surgical intervention. It also led to the development of a safer technique, cryosurgery.

The discovery of inhalational anesthesia is often attributed to serendipity. It is true that Humphry Davy, an English chemist, discovered in 1799 that inhalation of nitrous oxide caused him to become insensitive to pain. However, his suggestion that it might be useful in surgical operations was overlooked. The actual adoption of nitrous oxide as an anesthetic for surgery followed an accident that occurred at a public demonstration of the effects of the gas given for entertainment. When the lecturer called for volunteers to take the gas, a young man named Samuel Cooley responded. In reaction to the gas, Cooley became pugnacious and in the confusion that resulted he tripped and fell to the floor. As a result he acquired a deep cut in one of his legs which gave rise to a pool of blood on the floor under his seat. Although Cooley felt no pain until the effects of the gas wore off, a dentist friend named Horace Wells, who had accompanied him to the demonstration, took notice of what transpired. Wells perceived the significance of what he observed and shortly thereafter performed numerous painless dental extractions using nitrous oxide as an anesthetic (41).

The use of ethylene as an anesthetic agent was also largely the result of an accidental observation. Crocker and Knight in 1908 had demonstrated that carnations wilted when brought into the city because of the presence of illuminating gas, which contained about 4% ethylene. These observations stimulated an investigation in 1918 by Luckhardt and Thompson to determine the effect of ethylene on animal life. Although animals appeared to be lifeless when the gas was administered, they later recovered. In this way ethylene was discovered to be an effective anesthetic (33).

Accounts of serendipity are also scattered throughout the literature in obstetrics and gynecology. The discovery of the cause of puerperal fever by Ignaz Semmelweis in 1847 was due to a keen observation and an unfortunate incident. Semmelweis was puzzled by the fact that the maternal mortality rate was significantly higher among patients attended by physicians and medical students rather than by midwives. Although he attended postmortems of the dead women, he could find no explanation. However, when a coworker died of septicemia after performing an autopsy on a woman with puerperal fever, Semmelweis noted the similarity of the pathologic changes in the two cases. He concluded that puerperal sepsis was contagious and that it was transmitted to the mother

from the autopsy room by the unclean hands of the examining physician. The mortality rate markedly declined after he ordered scrubbing and disinfection of the hands by all maternity attendants. It is ironic that in 1865 Semmelweis died of the disease he had elucidated (33).

The effectiveness of the knee-chest or Sims position in the repair of vesicovaginal fistulas was discovered accidentally in 1855 by J. Marion Sims, a young American surgeon, while he was manually correcting a retroversion of the uterus. The enthusiasm which Sims experienced in making this discovery is best conveyed in his own words:

"To replace the dislocated organ, the patient (covered with a sheet) was placed on the knees with the pelvis elevated, and the thorax depressed. . . . My middle finger is more than half an inch longer than the index, but it could not be used without its fellow; and thus the two were passed, and in a few seconds, I could not touch the uterus, or even the walls of the vagina, and the fingers were swept around as it were 'in empty nothingness,' which was to me at the moment a most puzzling mystery. . . . While I stood doubting and wondering, my patient, now easy, threw herself down on her side, producing thereby a sudden escapement of air from the vagina; and thus the whole mystery of the accidental reduction of the dislocated uterus was explained on the principle of atmospheric pressure. . . . When the patient was in the position described, there . . . [was] a natural tendency of the pelvic viscera to gravitate towards the epigastric region . . . [allowing] the air to rush into the vagina under the palmar surface of the fingers, where, by its mechanical pressure of fifteen pounds to the square inch, this canal was dilated like a balloon . . . and I said to myself, 'If by this position the atmospheric air can be made to dilate the vagina to such an extent, even with a force strong enough to reduce a dislocated uterus, why will not the same principle allow me to explore this region, and examine accurately any injury, or disease to which it may be liable?' Full of the thought I hurried home—and the patient (with vesicovaginal fistula) . . . was placed in the position described, with an assistant on each side to elevate and retract the nates. I cannot, nor is it needful to describe my emotions, when the air rushed in and dilated the vagina to its greatest capacity, whereby its whole surface was seen at one view, for the first time by any mortal man. With this sudden flash of light, with the fistulous opening seen in its proper relations, seemingly without any appreciable process of ratiocination, all the principles of the operation were presented to my mind" (46).

Sims' successful repair of the vesicovaginal fistula laid the foundation of gynecology as a specialty.

The use of the vaginal smear for the diagnosis of early cervical carcinoma ("Pap test") was the result of serendipity and a prepared mind. For many years Dr. George Papanicolaou studied the cellular content of the vaginal smear in an effort to establish the morphological variations produced by the hormonal effects of the reproductive cycle. During the course of these studies he discovered that cancer cells could be recognized in the human vaginal smear. The elucidation of the relationship of these malignant cells to the various types of uterine cancer and the demonstration of the vaginal smear as a reliable means for the diagnosis of early lesions were major contributions which have resulted in a decreased mortality rate due to the diagnosis of many cases of early cancer long before symptomatology or overt pathological abnormalities are present (35).

The discovery of many types of medical therapy occurred when the potentiality of an accidental observation was recognized, often by the patient rather than by the physician. The treatment of paroxysmal atrial fibrillation with quinidine was an outgrowth of a patient's observation that quinine would stop his paroxysms (3).

The use of iodine in the treatment of Graves' disease was discovered when the great French clinician Trousseau absent-mindedly prescribed tincture of iodine to a patient with tachycardia due to Graves' disease, when he meant to give tincture of digitalis (3).

The effectiveness of phototherapy in lupus vulgaris was discovered accidentally by a Berlin watchmaker with lupus which was cured after using high power lenses near a window which allowed the sun's rays to focus on the affected area of his face (18).

The idea that rheumatoid arthritis might be reversible occurred to Dr. Hench of the Mayo Clinic in 1929 when a patient told him that his arthritic manifestations disappeared after jaundice suddenly developed.

This observation spurred the search for an anti-rheumatic agent (5).

The use of ephedrine sulfate in the treatment of myasthenia gravis was discovered accidentally in 1930 before the advent of Neostigmine. Dr. Harriet Edgeworth was a myasthenic who happened to take ephedrine to relieve concomitant allergic symptoms. She observed that the drug had a beneficial effect on the myasthenia. As a result, for the next few years ephedrine was the best drug for therapy. However, since 1935 it has been used only as an adjunct to treatment (34).

Thus far we have seen that the scientist with a "prepared mind" must possess great powers of observation as well as curiosity. Lack of these characteristics was responsible for many examples of lost serendipity. Contaminated cultures were discarded and fogged photographic plates disregarded. However, astute observers were able to translate such ordinary happenings into something new and revolutionary. In part this was made possible by a background of pertinent knowledge which enabled them to comprehend the significance of the accident. Furthermore, such investigators had sufficient curiosity to treasure their exceptions and to follow them up. Experimental problems were provisionally dropped in order to pursue a new line of research suggested by the unanticipated clue. Wangensteen has stated that "Maintenance of a child-like wonder is the best preparation of the mind for the investigator."

The successful serendipitists have also had the insight to realize the potentiality and applicability of their discoveries. Such an attribute might be called opportunism. Pasteur, Spiller, and Beaumont all possessed it and thus they were able to see far beyond the confines of an isolated circumstance.

Another indispensable characteristic of the prepared mind is receptivity. The prepared mind must be an open mind, free from preconceptions and rigid adherence to fixed ideas. The investigator must not dismiss the occasional rare observation which does not fit into the established plan. Neither must he make the facts fit the preconceived idea. Because the truths of science are all provisional, "incongruous" observations which are investigated and not discarded may either disprove previously held theories or yield new theories. Lister, in a graduation address to medical students, warned them against blindness to new ideas:

> "In investigating nature, you will do well to bear in mind that in every question there is the truth, whatever our notions may be. This seems, perhaps, a very simple consideration, yet it is strange how often it seems to be disregarded. I remember at an early period of my own life showing to a man of high reputation as a teacher some matters which I happen to have observed. And I was very much struck and grieved to find that, while all the facts lay equally clear before him, those only which squared with his previous theories seemed to affect his organs of vision. Now this, gentlemen, is a most pernicious, though too prevalent, frame of mind" (31).

Today the scientific method consists of the formulation of a working hypothesis, verification or rejection of the hypothesis by experimentation and observation, followed by arrival at a conclusion. "Because the methods and assumptions on which a systematic investigation is built selectively focus the researcher's attention, to a certain extent they sometimes constrict his imagination and bias his observations" (2). Claude Bernard insisted that, although a hypothesis is essential in the planning of an experiment, once the experiment has begun the investigator should forget his hypothesis, for it may lead to perceptual blindness:

> "When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted" (5).
>
> "Men who have excessive faith in their theories or ideas are not only ill-prepared for making discoveries; they also make poor observations" (4).

One interesting study has reported that two able scientists independently observed the chance phenomenon of fioppiness in rabbits' ears after intravenous injection of the enzyme papain, but both missed making a discovery because they shared the established scientific

view that cartilage is a relatively inert tissue. Eventually one of the scientists did go on to make a discovery which repudiated this view, but for a long time even he had been blinded by his preconceptions (2).

The importance of chance in medical discoveries is seldom realized, and is often neglected in treatises on the scientific method. Beveridge states, "Probably the majority of discoveries in biology and medicine have been come upon unexpectedly, or at least had an element of chance in them, especially the most important and revolutionary ones" (4).

Serendipity occurs in small discoveries as well as in revolutionary ones. However, its prerequisites of astute observation, curiosity, insight, opportunism, and receptivity are the same in both instances. Accounts of accidental discoveries occasionally appear in the daily newspapers. For example, recently a layman, after learning from an icthyologist that his goldfish had consumption, happened to throw them into a tank containing snails and algae. To his great surprise they were cured. A subsequent investigation at the city hospital revealed that an algae derivative was antituberculous and protected guinea pigs from contracting the disease (32).

It is unfortunate that many accounts of serendipity are not reported because the scientist does not wish to attribute his success to an accident. In fact it is likely that in order to create an image of logic many cases have been buried intentionally by investigators who refuse to concede that human frailty was a factor in their discoveries. Furthermore, the form in which discoveries are reported in scientific journals tends to conceal the role which chance may have played. As a result, the literature on serendipity is meager and case histories are not readily accessible.

The scientist ought to realize that "chance favors only those who know how to court her" (Charles Nicolle) (4). It is therefore not insulting to the integrity of a discoverer to admit that his discovery was accidental, for serendipity does not depend entirely on chance (42). It involves both the phenomenon to be observed and the appreciative, intelligent observer. Chance merely provides the most suitable circumstances, but it must be recognized opportunely and turned to advantage. This can be accomplished only by means of a creative intellectual process.

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Benjamin Rush's Medical Thesis, "On the Digestion of Food in the Stomach", Edinburgh, 1768*

Translated and with an Historical Introduction by DAVID F. MUSTO, M.D.†

Historical Introduction

BENJAMIN Rush concluded his student days with the publication and defense of a dissertation. A medical thesis not only fulfilled a formal requirement for graduation with an MD at Edinburgh, but it also had a number of other functions. In most cases one of these, the advancement of knowledge, can be passed over rather quickly. The writings more often demonstrated the bibliographic rather than the scientific skills of the aspiring doctor of medicine. The subject of the dissertation usually was suggested by a faculty member who then occasionally offered advice during the development of the thesis. On the fateful examination day the student defended his thesis before the faculty. At some schools a few days residence and payment of tuition sufficed for a diploma. (Of course, a doctorate was not required for the practice of medicine.) At other schools, e.g. Edinburgh, the MD degree could be obtained in no way other than by the presentation of a thesis (1). Having assumed the cost of printing, the author distributed copies of his thesis to friends and potential medical patrons. The work was prefaced by a dedication which afforded the candidate an opportunity to thank the person or persons who had assisted him. Benjamin Rush listed seven men ranging from his brother, Jacob Rush, to Benjamin Franklin. Lest anyone think the list of names to be superfluous or insignificant, it should be noted here that the sequence of two names, Dr. William Shippen, Jr., and Dr. John Morgan, produced perhaps the largest impact of Rush's thesis. In sum, a thesis represented new knowledge, the fulfillment of a requirement, advertisement and appreciation, all bound together in a literary form peculiar to the medical profession.

The events leading to Benjamin Rush's presentation in 1768 of *de Coctione Ciborum in Ventriculo* are simple to relate (2). He was born in 1746 and graduated from the College of New Jersey (Princeton) in 1760. After some hesitation in choosing a career, he became apprenticed to the leading Philadelphia practitioner, Dr. John Redman, whom he served until 1766. While an apprentice he attended Shippen's anatomical lectures (1762) and medical courses, including Morgan's lectures on materia medica at the recently opened College of Philadelphia. In November 1766, with the approval of his mentors and the apparent promise of the Chair of Chemistry in the college, he sailed for Edinburgh, home of the pre-eminent medical school of the English-speaking world. Having entered its most glorious phase, this school rivaled any in Europe and had already attracted many students from colonial America, including Shippen and Morgan. At Edinburgh Rush attended lectures of William Cullen, Joseph Black, Robert Ramsay and Alexander Munro *secundus*, among others, and concluded his two-year residence with a thesis.

Rush traveled in England and France until May 1769 when he sailed for Philadelphia. On the first of August 1769 he was elected

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DISSERTATIO PHYSICA
INAUGURALIS,
DE
COCTIONE CIBORUM
IN VENTRICULO:

QUAM,
ANNUENTE SUMMO NUMINE,
Ex Auctoritate Reverendi admodum Viri,
GULIELMI ROBERTSON, S. S. T. P.
ACADEMIÆ EDINBURGENÆ PRÆFECTI;
NEC NON
Amplissimi SENATUS ACADEMICI consensu,
Et nobilissimæ FACULTATIS MEDICÆ decreto;
PRO GRADU DOCTORIS,
SUMMISQUE IN MEDICINA HONORIBUS ET PRIVILEGIIS
RITE ET LEGITIME CONSEQUENDIS;
Eruditorum examini subjicit
BENJAMINUS RUSH, A. M.
PENSYLVANIENSIS.
Prid. Id. Junii, hora locoque solitis.

Omnino, scientia ex naturae lumine petenda, non ex antiquitatis obscuritate. Nec refert, quid factum fuerit; illud videndum, quid fieri possit. Verulam. Oper.

EDINBURGI:
Apud BALFOUR, AULD, et SMELLIE,
Academiae Typographos.
M,DCC,LXVIII.

For
Mr. Mc. Ilvaine
from his humble
Servant
the Author.

FIG. 1. Title page and author's inscription to William McIlvaine, a medical graduate of the University of Edinburgh in 1771, whose thesis was entitled, *De anorexia*. Dr. McIlvaine (1750–1806) was elected a Fellow of The College of Physicians of Philadelphia in 1791.

the College of Philadelphia's Professor of Chemistry, thereby becoming the first chemistry professor in America. The course of his later life is well-known. He was active in various roles—as medical practitioner, republican leader and social reformer—and was a confidant of Jefferson, John Adams, Rittenhouse and others. By the time of his death at age 69 he had become *doyen* of American medical theorists and practitioners, but his life was stormy, concocted of many a bitter feud in almost every area of activity. He tended to question the motivation of his opponents and was, by and large, morally certain of every position he adopted. The great battle which embittered him for many years evolved from his treatment of Philadelphians during the Yellow Fever epidemic of 1793 when he advocated frequent, voluminous blood-lettings and thorough purgation as the specific treatments. True to character, he maintained the wisdom of his therapy against all critics. Having castigated the doubters, he eventually found himself the target of the witty, devastating and libeling publications of William Corbett, one of whose labels for Rush was "the Philadelphia phlebotomist". His practice declining, Rush became lonely and sour but never wavered in his convictions.

A foretaste of battles to come had occurred when, 23 years old and newly returned from Edinburgh, Rush began a campaign against those older practitioners who disagreed with the medical theories of the celebrated Dr. William Cullen (1712–1790), Edinburgh's leading medical theorist who incidentally had guided Rush in the choice of his thesis topic and subsequent investigations into digestion, and to whom Rush had formed a strong emotional attachment (3). Rush long maintained admiration for his Edinburgh professors. "The whole world," he once wrote during his Scottish studies, "does not afford a set of greater men than are at present united in the college of Edinburgh" (4). He described his teachers as instigating "a revolution in physic" who had "now exploded . . . the old doctrines of the blood, nerves, etc." (5). His highest praise was reserved for Cullen, ". . . the great,

the unrivaled Dr. Cullen . . . going on unfolding each day some new facet to us in the animal economy" (6). Writing to John Morgan the year of the thesis' publication, Rush apostrophized Cullen, "Illustrious oracle of human wisdom, live—live forever"! (7)

Of Rush's instructors, three figure prominently in the text of his thesis: Cullen, Joseph Black, and Robert Ramsay. In rough summary Cullen, Professor of the Theory of Physic, taught that disease was not an imbalance of the four humors, as the medical profession commonly thought, but rather was an excess or paucity of nervous tension in the body, transmitted through the nerves and acting upon the muscles. Should a disease be caused by excess nervous tension, some relaxing procedure such as phlebotomy might be performed or, alternatively, an astringent could be administered to increase the tension. Much of this theory was stated, but less definitively, by Cullen's old teacher, Boerhaave. Cullen combined with theorization a striking talent for classification, and on his exhaustively complete nosological tables rested much of his contemporary reputation.

The ingenious Joseph Black (1728–1799), holding the Chair of Chemistry at Edinburgh, came second in the esteem of Rush who was interested in his lectures not only because Rush expected to hold the Chair of Chemistry at Philadelphia upon his return, but also because he thought he could be useful to America by importing new industries based on chemistry, e.g. porcelain manufacture (8). Black's work was of more lasting value than Cullen's: Black is credited with inaugurating the present era in chemistry with his elegant experiments demonstrating that some heated substances do not gain weight. This result served later chemists as a basis for disproving the phlogiston hypothesis of a material heat. In addition, Black isolated carbonic acid from quicklime, associating it with the gas present in expired air, and made the fruitful distinction between the temperature of a body and the amount of heat it contains.

Dr. Robert Ramsay, whose own thesis *de Bile* is quoted in Rush's thesis, graduated from Edinburgh with an MD in 1757 and 10 years later was appointed the first Regius Professor of Natural History and Keeper of the Museum of the University. Little is known of his work or life. He died in 1779.

After about a year's residence in Edinburgh the topic of Rush's dissertation had been chosen and in January 1768 he informed John Morgan:

> I am now busily employed in translating my thesis. The subject of it is digestion, in which I hope to publish a discovery that will admit of some useful inductions in pathology and the practice of physic. I shall beg leave to prefix your name to it together with Dr. Franklin's, Dr. Black's, Dr. Shippens [sic] and Redman's. The thesis will contain little more than a few experiments on which the whole of my doctrine is founded (9).

Standing near the center of the many medical and philosophical disputes of the 18th century, the problem of digestion contained in its core the remarkably difficult question of how one substance changed into another (10). The answer was one of the chief objects of natural philosophers. The approach Rush took, under Cullen's guidance, illuminates the state of anatomico-physiological knowledge and the assumptions these men held when approaching this universal problem. At hand were two general categories of information: the discoveries based upon observation and experiment up to that time, and the intellectual models for understanding the information and assimilating it into a comprehensible system. Eighteenth-century physicians were nothing if not sensitive to a need for encompassing systems of explanation or at least classification.

As for available information, Rush knew many things. Saliva and gastric juice had been distinguished and bile and pancreatic juice were known to be admitted to the duodenum. With the latter two fluids a number of experiments had been conducted to determine taste, change in the presence of other substances, their alkalinity or acidity, and their effect on raw or chewed food. The conclusions, however, were not definitive. The anatomy, including the stomach muscles, lacteals, and

gross innervation, had been pretty well demonstrated. Writers agreed on a few essentials: food was chewed in the mouth and mixed with saliva, then it entered the stomach where some sort of action turned a portion of the material into chyle or at least prepared it for that change in the small intestine from which it passed into the blood and attained its object by replenishing the body humors or whatever the writer believed to be the body's constituents.

The crux of the matter lay in the mysterious change taking place in either the stomach or the duodenum. Anyone theorizing on the change of food into chyle was faced with this baffling event, and to explain so fundamental an occurrence physicians inevitably fell back on their general philosophical or religious orientation. No matter how finely ground be the food, the transformation did not seem to Rush to be simply a mixing or the result of chewing (although, to be sure, a few thought it was just that), but rather "a kind of generation," as John Hunter stated two decades after Rush's thesis, "in which two substances become a third" (11).

What could change substances? Many at this time, and we must include Rush in the group, could not conceive how a material agent could change a material substance into something so different as in the case of raw food becoming "sweet chyle" and *a fortiori* the very humors themselves. Although Rush does not explicitly state that he is invoking a "vital principle"—a sort of animal force which accomplishes the arcane processes of living beings—he evidently does not accept material and physical causes as explanations of all animal processes. For example, when reproaching the mathematicians for their failure to explain physiology he writes: "The human body enjoys so individual a construction that it refuses subjection to mechanical laws" (12). And his attempts at refuting mathematical, chemical and physical forces can be understood only by assuming Rush adopts a vitalistic explanation of fermentation and chylification. Discussing fermentation, Rush says that "everyone hesitates . . . to explain the causes upon which this remarkable action of nature depends. So far these causes lie hidden in shadows and will, perchance, lie so hidden forever" (13).

A "vital principle" is a handy mental construction for anyone who is confident it has explanatory power. In reading Rush's thesis it does not appear that he closed his eyes to further investigation by the adoption of any immaterial agent, but that its tacit use was the best he could do considering his understanding of the alternatives.

One alternative was atomism and the closely allied material explanation of the iatro-chemists and iatro-physicists. Atomic theory, so appealing because of its picturability, simply stated that all substances were made of a few building blocks whose organization created their qualities. The chemists used as their model the solution, for example, of a metal in acid and its reprecipitation to demonstrate how radical change could be manipulated with common substances and in more familiar surroundings than the insides of an animal. Physicists were impressed by the powerful forces of heat, compression, grinding and sifting.

None of these explanations satisfied Rush. He believed that a chemical solution or combination does not result in any *true* change, but that the substances involved assume different guises and actually are recoverable in each case. As for great pressures causing change in the stomach, Rush had at hand the rugged experiments of the Rev. Stephen Hales who had subjected to pressure the stomachs of recently killed animals and discovered that they burst at relatively low pressures (14). The argument of the pressure-theorists was that during life high pressures up to tens of thousands of pounds were obtainable according to the following reasoning: Borelli, the so-called father of iatro-mathematics, calculated that the flexor pollicis longus could produce a pulling force of 3,720 pounds and had a weight of about two ounces (15). Later theorists weighed the stomach (eight ounces)

and multiplied each ounce by about 1,800 pounds to calculate its "force"; the result was quite impressive. Haller, however, pointed out that the stomach is only a fraction muscle (16) and, furthermore, Rush declared, no matter how finely one grinds food it is still only finely ground food. Borelli, not himself narrow minded, envisioned a variety of agents operating in digestion besides pressure and grinding, e.g., a strong dissolving substance found in some fish stomachs. His intellectual descendants, however, were less eclectic and sought to find in mechanics alone an explanation to natural phenomena.

Some experimental work was useful to Rush in his examination of fermentation and bile. Concerning the latter he quotes mostly from Ramsay's thesis, published in 1757 (17). Ramsay described bile as having the property of converting acid or alkaline substances to a sweet taste without itself being either acid or alkaline. This finding promised to have important application in the process of digestion since here was a change similar to that of food into chyle. Neither Ramsay nor Rush could identify the property which enabled bile to do this, but Rush stated in his thesis that probably bile, suggested by many authors as playing an important role in digestion, was in fact the agent which ultimately changed food into chyle.

To reach the proper state for bile's action, Rush reasoned, food must undergo fermentation, considered by some writers to be identical to digestion. Fermentation was an attractive explanation for digestion because it was caused by a substance, ferment, which produced new substances, alcohol, acid and putrid matter, which were not reversible into their origins. Moreover, the active agent seemed to be a vital activity mysterious enough to satisfy those who felt that "ordinary" matter could not do the job of substantive change. At the time Rush was writing, three kinds of fermentation were described. The first produced alcohol which, if the fermentation were allowed to continue, would result in acid, e.g., vinegar, and finally the substance would be fermented to rottonness. Rush's emetic experiments were directed toward proving that the stomach's acidity resulted from fermentative action. A detailed analogy between the stomach and a still was established so that acetous fermentation would seem inevitable. In an acid state food was ready for the remarkable action of bile which completed digestion by transforming the acid food into bland chyle.

A semantic problem seems to arise with the definition of "digestion". Rush used the word to indicate complete transformation of food into chyle. He required for the process, therefore, two stages: fermentation to an acid state, and the action of bile to transform the acid state into chyle. Thus it is not correct to say—as have some writers in discussing Rush's dissertation—that Rush thought digestion was "acetous fermentation", for he thought that fermentation was only the first step in the process and could not in itself produce the chyle.

The long-standing use of analogies to explain digestion evoked John Hunter's well-known exclamation:

> Some physiologists will have it, that the stomach is a mill, others, that it is a fermenting vat, others, again, that it is a stew-pan; but, in my view of the matter, it is neither a mill, a fermenting vat nor a stew-pan; but a stomach, gentlemen, a stomach (18).

Analogies were particularly useful at this time, however, since direct observation of a living stomach did not come until Jacob Helm's investigations at the close of the century (19).

Even today the commonly employed nasogastric tube has its distinct limitations when anyone tries to obtain uncontaminated gastric juice. Pure gastric juice can be collected with greatest assurance by a Pavlovian-type operation, separating the stomach and esophagus and making an exterior opening from the stomach—a difficult technique and not suitable for humans. To keep out the admixture of saliva, bile and pancreatic juice was a technical problem which Rush admitted he could not solve. For his purpose, however, he only wanted to determine whether the food was rendered acid after a few hours in the stomach.

He considered himself to have illustrated so well that the stomach was a fermenting vat that, there being no local source of the acid, what might be detected could come only from fermentation. Since the factors promoting acid secretion in the stomach vary according to time of day, food intake, age and personality, and since the significance of the various cells lining the stomach cavity were not known, it was difficult to establish with tools available to Rush's contemporaries that acid is secreted from the stomach wall in the absence of food.

Our admiration for Rush's zeal to establish the nature of digestion is raised by the nature of his experiments. After taking an alkaline salt to destroy any acidity left over from the last meal, he induced vomiting three hours later and tested the vomitus. It was always acid. In later years Rush said he would pay more attention to other theories when their authors had taken as much tartar emetic as he had (20). He must have been persuasive as well as determined because he was able to talk a friend into an experiment or two as a control to answer those who might think his own stomach unusual or diseased. A more restrained experiment concluded his reported series: he mixed meat with water and found it fresh after 20 hours in a sand bath; when mixed with saliva, fresh meat revealed signs of fermentation in five hours and acid reaction in seven hours, and after twelve hours of warming with saliva it emitted a bad odor (21). Here, he felt, was proof of the fermentative power of the juices which would be mixed with food in the stomach. Rush does not allude to David MacBride's almost identical experiments, published in 1764 which were designed, as were Rush's, to establish the fermentative power of saliva (22).

Rush wrote his thesis in the standard literary form, beginning it with an epideictic review of primeval man's eating habits and various latter-day dietary customs. This section is for the most part suspiciously close to Albrecht Haller's introduction to the subject of digestion in *Volume Six* of the *Elementa Physiologiae* which had been published two years prior to the thesis (23). Not only is virtually every historical and anthropological fact mentioned by Rush contained in Haller's volume on digestion, but also, quite unlike Haller, Rush gives only the least number of references, and these incompletely. In one case he may have faltered in copying a footnote. Haller mentions that some Persians live on raw dates, and in Haller's footnote appears the reference to Kämpfer's *Amoenitates Exoticae* (24). Haller then expands the footnote by adding that some Egyptians also live on dates and gives as reference the Swedish naturalist and traveler, Frederick Hasselquist (25). Rush states in his thesis that Persians exist only on dates, but gives as reference not Kämpfer but Hasselquist, who neither traveled to Persia nor commented on Persian eating habits. Incidentally, Rush drops the page reference.

In the following section Rush reviews doctrines to be rejected, then gives his own solution to the problem of digestion and concludes with some experiments justifying it. The last word, appropriately, is an encomium to his advisor, Professor Cullen. Towards the end Rush comments that he had planned to talk briefly about pathology (as he had written to Morgan), but that lack of space forbade it. The complete text was written out in English and translated into Latin. Although Rush left in his personal letters several remarks to the effect that Latin was not his forté, I have found no evidence that the translation was not his own (26).

The dissertation carried little influence. It was not chosen for inclusion in the *Thesaurus Medicus*, printed in Edinburgh every few years and containing leading theses by graduating students. I find it rarely mentioned in later works devoted to digestion, although Rush's vomiting experiments usually raised a comment from biographers and historians. In a eulogy of Rush the prominent London physician John Coakley Lettsom appraised the thesis with sentiments more a tribute to their friendship than to Lettsom's acumen. The thesis, according to Lettsom, was "a performance so accurate, and so ingenious and lucid in diction, as to have placed him in a prominent

and honourable point of estimation in that Celebrated School, which a Munro raised, and a Cullen supported and dignified" (27). Rush himself later changed his mind about the subject as the result of a thesis by John Young, one of his own students at the University of Pennsylvania, and decided that fermentation did not have a place in digestion (28). Also, in Rush's later works the function of bile became more associated with mental processes than with digestion (29). His increasing absorption with various other medical problems and contentious social questions apparently left him little time for further research into digestion.

The strongest impression made by the dissertation was reserved for the order of names in the dedication. It seems that in this early period of our national history medical professors were jealous of their positions and eminence and thus did bitterness arise over the question of who was the founder of the College of Philadelphia's medical school. Dr. William Shippen, Jr., had given the first lectures and suggested the formation of a medical school in 1762, but in 1765 Dr. John Morgan became the first physician elected Professor in the College. Morgan's historic *Discourse on the institution of medical schools in America*, in which he attempted to garner for himself the laurels of founding the first medical school in the English colonies, slighted Shippen's earlier proposals. Wounded by Morgan's arrogance, Shippen nevertheless did join the faculty later as Professor of Anatomy, but Morgan had gained the upper hand in the battle for prestige (30). So bitter was the feeling in this affair that when Rush dedicated his thesis to, among others, Shippen and Morgan, the sight of Shippen's name above his own roused Morgan to fury. His displeasure apparently was transmitted in 1768 to Rush who replied placatingly:

> I am sorry to find I have not followed the order in the names which you hint at, in the dedication of my thesis. Had your letter arrived sooner, your name would have been first. But I thought it a matter of no consequence. Dr. Shippen was my oldest friend and master, and this was the only reason I put his name before yours. The position of the names in my dedication by no means indicates the degree of respect or affection... I hope therefore, my good friend, you will overlook my omission in placing your name after Dr. Shippen's. My thesis has been read, and is now I dare say forgot (31).

Such an error might have been due to Rush's habitual insensitivity. Being far away, however, he was perhaps out of touch with the Philadelphia rivalries and consequently may not have realized the significance of the order of names. He wanted the position as Professor of Chemistry at the College of Philadelphia; therefore Morgan, who had originally promised it to him and whose recommendation was essential for obtaining the position, would be the last person Rush would want to offend. But that he had indeed offended him is obvious in Morgan's long, angry and grammatically confused letter a year later:

> Why, I had informed you, I could not approve of your having placed my name in the manner you had done in the dedication of your thesis, for which indeed you made some sort of apology. I should have thought it sufficient, if I could be perswaded [sic] that it had been accidental, & that you gave no room for charging you with having paid a compliment to another at my expense, designedly or knowingly.
>
> In no letter that I ever received did you declare it to be accidental or undesigned, as your last asserts. All that you wrote to the purpose was, that you did not think I would have taken it amiss, or it should have been otherwise. But how you could imagine I would take it in good part is beyond my comprehension ...
>
> ...The dispute of seniority, and precedency established thereupon, which had subsisted between Dr. Shippen and myself was, at a full meeting of the Trustees of the College, determined in my favour. I told you that Dr. Kuhns [sic] (32) behaviour which had so sensibly affected me, tended to support Dr. Shippens [sic] pretensions to precedency, although determined as above; and further that the order in which you had placed our names had the like tendency as far as any thing you could do, would [sic] support a claim already decided to be groundless. I urged that on this acc't it was more necessary I should be made acquainted with the motives of your conduct whose cause I had so warmly espoused, for if you still thought it right, I was exerting myself for one who so far from subscribing to the suffrage of the Trustees might do all he could to weaken it, & to break through the established order of the College. What is this less than disputing precedency with me yourself? For if you do it in favour of any junior professor you do so for yourself, although

you acknowledge yourself to be chiefly indebted to me for the Professorship of Chymistry, if you do obtain it (33).

Nevertheless, upon his return Rush was elected Professor of Chemistry and he remained a firm supporter of Morgan thereafter.

Acknowledgments

It is a pleasure to acknowledge the generous assistance I received in preparing this paper from Miss Madeline E. Stanton, Librarian of the Historical Collection, Yale Medical Library; Miss Elizabeth H. Thomson, Research Associate, Department of the History of Science and Medicine, Yale University; Miss Janet F. Oswald, Librarian of the Pennsylvania Hospital; Mr. C. P. Finlayson, Keeper of Manuscripts of the Library of the University of Edinburgh; and Dr. W. B. McDaniel, 2d, Curator of Historical Collections, Library of the College of Physicians of Philadelphia. The Ridgway Library gave permission to quote from Morgan's letter to Rush. I wish to express especial gratitude to Dr. Maria Wilkins Smith who provided me with a preliminary draft of the translation. I am responsible, however, for its final form.

In the translation of the thesis, Rush's footnotes are lettered and give the full citation when it could be located in an edition which might have been available to the author; translator's comments are bracketed. Rush himself rarely gave page references and never a full bibliographic citation; for example, the full Rush reference in "B" is "Haselquist's [sic] Travels." Notes by the translator which explain some facet of the text are numbered and are placed after the translation.

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4. Benjamin Rush to Jonathan Bayard Smith, 30 April 1767, *Letters* I, 41.
5. *Ibid.*
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13. *Op. cit.*, p. 19.
14. Stephen Hales, *Statical Essays* (3rd edition, corrected, London, 1769), II, 174–175).
15. J. A. Borelli, *De Motu Animalium* (Leyden, 1710), Pars Prima, Prop. 126, p. 137.
16. Albrecht Haller, *Elementa Physiologiae* (Leyden, 1766), VI, 274–275.
17. Robert Ramsay, "De Bile," *Thesaurus Medicus II* (Edinburgh, 1785), pp. 453–469.
18. William Hunter, *Two Introductory Lectures* (London, 1784), p. 95.
19. Bruno Kisch, "Jacob Helm's Observations and Experiments on Human Digestion," *Journal Hist. Med. & Allied Sciences* **9:** 311–328 (1954).
20. Rush's comments in 1796 were recorded by one of his students (Bates, *op. cit.*, p. 351).
21. Dr. Joseph Pringle, whom Rush quotes in other contexts, performed similar experiments but with opposite results and concluded that saliva retards fermentation (*Diseases of the Army* [5th edition, London, 1765] Appendix, Paper 4, Experiment 30, p. 335). Pringle was a man of many parts—social reformer, military physician, President of the Royal Society, etc. He befriended Rush during the latter's stay in London by inviting him to attend a small, select medical society which met at Pringle's home. As a token of his esteem, Rush edited with amplification the first American edition of *Diseases of the Army* (Philadelphia, 1810).
22. David MacBride, *Experimental Essays* (London, 1764), p. 13ff. MacBride experimented with lamb and many other substances in a fashion very similar to that of Rush.
23. *Cf.* Haller, *op. cit.*, pp. 189–213.
24. Engelbert Kämpfer, *Amoenitatum exoticarum*

politico-physico-medicarum Fasciculi V (Lemgo, 1712), pp. 736–737, 748–749.

25. Frederick Hasselquist, *Voyages and Travels in the Levant* (London, 1766), p. 261.
26. Benjamin Rush to Ebenezer Hazard, 27 June 1765, *Letters*, I, 16–17; Rush to Hazard, 8 November 1765, *op. cit.*, pp. 18–19; *Autobiography*, p. 42.
27. John Coakley Lettsom, *Recollections of Dr. Rush* (London, 1815), p. 4.
28. John R. Young, *An Experimental Inquiry into the Principles of Nutrition and the Digestive Process* (reprinted with an introductory essay by W. C. Rose, Urbana, 1959). Young mentions Rush's and MacBride's defense of the role of fermentation in digestion (pp. 36–39) but demonstrates that acetous fermentation does not take place in the stomach. Mr. Rose evaluates Rush's saliva experiment (V) as "incredibly stupid" (p. xix). Rush's concession to Young's conclusions is recorded by a student, William Darlington (*Rush's Lectures on the Institutes of Physic 1803–1804* [Manuscript, Library of the College of Physicians of Philadelphia], I, 81).
29. For example, the following excerpt from Darlington's notes contains his full reference to bile from Rush's lecture on digestion. Consider the interesting assumptions which probably underlay Rush's psychosomatic reasoning: "The *Bile* is a septic product, but proves antiseptic when formed; so is nitre. Anger promotes the secretion of bile. A young man puked a gill of bile, after an insult which he could not resent." (*Op. cit.*, p. 87).
30. Carl and Jessica Bridenbaugh, *Rebels and Gentlemen* (New York, 1962), pp. 277ff.
31. Rush to Morgan, 27 July 1768, *Letters, I*, 62.
32. Adam Kuhn (1741–1817) obtained his MD at Edinburgh in 1767. He was Professor of Materia Medica and Botany at the College of Philadelphia. Kuhn broke with Rush over the treatment of victims in the Yellow Fever Epidemic of 1793.
33. Morgan to Rush, 10 May 1769, *Rush Manuscripts*, Ridgway Library, Philadelphia, Pa.

Medical Dissertation on the Digestion of Food in the Stomach

By BENJAMIN RUSH

A. Genesis 9:3. Every moving thing that liveth shall be meat for you; even as the green herb have I given you all things.

B. Frederick Hasselquist, *Voyages and Travels in the Levant* (London, 1766). (On page 261 Hasselquist remarks: "The fruit or dates are commonly eaten. In upper Egypt many families subsist almost entirely on dates. . . ." See Historical Introduction for Rush's possible confusion of references.)

C. Pitton de Tournefort, *Relation d'un Voyage du Levant* . . . (2 v., Paris, 1717). (I have examined several editions of the *Voyage* without being able to verify this reference.)

D. The celebrated Cocchi, professor of anatomy in the school of Florence, warns in his lecture on the Pythagorean eating habits: "But what should fully perswade [sic] everyone that thinks justly of the Salubrity and Power of Vegetable Diet, is the Consideration of the horrid Effects of Totally abstaining from such a Diet, unless it be for a very short Time: Accounts of which we meet with fully and faithfully recorded, in the most interesting and most authentic Narrations of human Affairs, Wars, Sieges of Places, long Encampments, distant Voyages, the Peopling of uncultivated and maritime Countries, remarkable *Pestilences*, and the Lives of illustrious Men, administer to anyone who understands the Laws of Nature, irresistible Evidences of the bad and venemous Consequences of a Diet contrary to that of fresh Vegetables . . ." (Rush quoted Cocchi in Italian; this translation was taken from: Antonio Cocchi of Mugello, *The Pythagorean Diet, of Vegetables only, conducive to the Preservation of Health, and the Cure of Diseases. A discourse delivered in Florence in the month of August, 1743.* Translated from the Italian [London, 1745], p. 69.)

E. John Pringle, *Observations on the Diseases of the Army* (5th ed., London, 1765), Appendix, paper 3, Exper. 25. p. xxxvii.

F. *Ibid.*, part 3, chapt. 7, p. 287 ff., "Observations on the Jail, or Hospital fever." (Nothing here seems to support Rush's statement.) Appendix, Paper 4, Exper. 27, p. xli. Pringle demonstrates that sugar does not promote putrefaction.)

G. Virgil *Georgics* iii. 379–380. "Here they spent the night in revelry, and cheerfully made up for absent cups of wine with draughts of the acid service-berry."

H. *Ibid.* 461–463. "As the Bisaltae are accustomed, as well as the fierce Geloni when they flee toward the Rhodope and in the wilderness of the Getae—To drink milk curdled with the blood of horses."

I. Pringle, *op. cit.*, Appendix, Paper 4, Exper. 29, 36, pp. xlviii, lviii.

J. G. E. Stahl, *Theoria Medica vera* (Halle, 1708), p. 371. "Various simple experiments prove that saliva has a fermentative nature."

K. Stephen Hales, *Haemastaticks* (3rd ed. cor., London, 1769), II, 174–175.

L. J. B. Van Helmont, *Opera Omnia* (Frankfort, 1682), pp. 111, 119.

M. [P-J. Macquer], "Putrefaction," *Dictionnaire de Chymie* (Paris, 1766), II, 335–339.

N. Johannes Baptista Du Hamel, *Regiae Scientiarum Academiae Historia* (2nd ed., Paris, 1701), p. 180. "Lest the excrement of living things seem unworthy of chemical analysis, it can be generally stated that animals living on flesh excrete material containing a considerable amount of oil and volatile salt, containing, also, a little *acid*." (Italics were added by Rush.)

O. Albrecht Haller, *Elementa Physiologiae*, Vol. 6 (Leyden, 1766), p. 316.

P. "According to Helmont's observation, there seems to be another use of bile, because some sort of acid is certainly always found in the stomach of herbivorous animals. After a draught of bile, however, nothing whatever of acid can be found either in the intestines or in purged feces. Hence it is established through the previously adduced experiments that any vegetable acid, when drenched with bile, is so changed that neither by taste nor by the curdling of milk does it show itself as acid. Therefore bile changes the acidifying quality of food, but it does not seem to me that this is done by a mixture of anything alkaline or subalkaline, neither of which is found in bile, nor is it done by the mingling of any heating or putrefying element in the bile." Robert Ramsay, "De Bile" in *Thesaurus Medicus*, vol. 2, pp. 468–469 (Edinburgh, 1785). (The reference to Van Helmont is found in "Sextuplex Digestio Alimenti Humani," *op. cit.*, pp. 198–214.)

TO THAT MOST OUTSTANDING PERSON

BENJAMIN FRANKLIN, L.L.D. F.R.S.

OF THE PROVINCE OF PENNSYLVANIA

WORTHY DELEGATE TO THE BRITANNIC COURT,

KNOWN FAR AND WIDE,

DISTINGUISHED BY LETTERS AND BY HABITS,
AND OF THE ARTS AND SCIENCE
A PATRON, PROTECTOR AND AUTHOR;
EMINENT
BECAUSE OF THE GREAT LOVE
IN WHICH HE HOLDS HIS COUNTRY,
CITIZENS AND FRIENDS;
AND
TO THE EXTRAORDINARY PRECEPTORS
JOSEPH BLACK, M.D.
PROFESSOR OF CHEMISTRY IN THIS COLLEGE,
FELLOW OF THE
COLLEGE OF PHYSICIANS OF EDINBURGH,
BOTH FOR THE
ACUTE INSIGHT AND EMINENT LEARNING
WHICH SCIENCE,
EMBELLISHED BY HIS DISCOVERIES
WILL ALWAYS ACKNOWLEDGE WITH GRATITUDE,
AS WELL AS
FOR ALL THE GIFTS OF THE MIND
WHICH ENRICH THE PHILOSOPHER,
PHYSICIAN AND MAN
WITH EQUAL CONSPICUOUSNESS;
AND TO
JOHN REDMAN, M.D.
THE MOST EXPERIENCED PHYSICIAN
IN THE CITY OF PHILADELPHIA,
OF BLAMELESS LIFE,
WHO FIRST OPENED FOR ME
THE FONTS OF MEDICINE;
AND ALSO
TO THOSE DISTINGUISHED MEN
WILLIAM SHIPPEN, M.D.
AND
JOHN MORGAN, M.D. F.R.S. &C.
EMINENT PROFESSORS
IN THE COLLEGE OF PHILADELPHIA
THE FORMER OF ANATOMY,
THE LATTER OF MEDICINE;
AND FINALLY
TO THOSE MOST LOVED OF FRIENDS
JONATHAN SMITH, A.M.
NO LESS FROM LETTERS THAN FROM HABITS
REMARKABLY AGREEABLE,
ONCE MY CLASSMATE IN THE
COLLEGE OF NEW JERSEY;
AND
JACOB RUSH, A.B.
DEAREST BROTHER
EVEN NOW IN HIS YOUTH
KNOWLEDGEABLE IN THE LAW
QUICK-WITTED, ELOQUENT AND VIRTUOUS;
BENJAMIN RUSH
DEDICATES THIS DISSERTATION

SINCE it is a regulation of this distinguished Academy that those who are candidates for highest honors in medicine must publish some illustration of their ability, I proceed in fear and trembling to offer this first product of my studies.

As I considered the various subjects of investigation, I decided to examine the digestion of food in the stomach—certainly a profound subject and one concerning which there is a variety of opinions among the most eminent authors. But before I begin, it will be useful to discuss a few matters concerning food generally.

Concerning Food in General

Everything which feeds and revitalizes the body is drawn from vegetables and animals. To these are added certain seasonings fetched, for the most part, from the depths of the earth.

Concerning Vegetable Food

Since without having been sought, produce was already created, it has been thought that the

descendants of Adam fed on them for a long period. For the soil, free from the hoe and uncut by plow, continued by itself to supply all these things. The field, as yet unaccustomed to cultivation, grew yellow with ears of corn. The early inhabitants of the earth, ignorant of how to till the soil or to yoke oxen, lived a happy life, enjoying the wealth offered them spontaneously by the earth. As yet unaware of how to rule by barbarous skills and capture animals with traps, they sought their sustenance only from the fruits and plants with which the Supreme Creator had generously filled their world. After the passage of some generations, when the population increased and when social bonds were forged, Ceres revealed her gifts and the art of cultivating fields began. Grassy plants, abundant in grains, supplied much of their food. Such plants were not exhausted by use but, with a little effort, were preserved for years around peoples' huts. Hence wheat, rice, maize and other grains appeared in the diet. Nor were men supplied only with these foods. Cows, goats and woolly flocks furnished milk from their full udders. Early histories report that for many generations man especially enjoyed these foods. That was the Golden Age! when men refused to assuage their hunger with meat and delighted in bloodless banquets!

Concerning Animal Food

The period when oxen were taken from the plow, or sheep were taken from the fold or seized in the mountains and used to supply bloody and cruel ritual banquets, is as yet uncertain. Every history, however, clearly reveals that from the creation of the world animals were condemned to the sacrificial knife so that, by tearing out and examining the viscera, men might ascertain the will of the Gods or might propitiate the divine anger. For many ages, however, men were loathe to defile their lips with blood and rejected the sacred meats. Some suggest that the use of meat developed just after the Flood when the inundated earth was not yet able to bear its usual fruit. Much weight is lent to this opinion by the well-known words of the Judaic Lawgiver (A).

Various animals are regarded as food in various regions. One man grows fat on beef, another one spits it out. In one area inhabitants eagerly devour horses, asses, goats, even dogs; in another place the people shrink from these foods in horror as if they were rotten. Here the sea casts its dwellers upon the shore, while in forests far removed from the sea men live on wild beasts only.

Among writers the most violent controversies are carried on as to whether man is naturally herbivorous or carnivorous. It does not seem irrelevant to give a little attention to this question. One can hardly deny that in every age some men have lived solely on vegetables. The date-palm is the Persians' only source of food (B). On fruit, water and goats' milk the Arabs live happily. Only raw cucumbers support the majority of Constantinople's citizens (C). Manioc affords the only source of food to the natives of the western isles, and many Scottish highlanders, who are hard workers living on onions and oats, come unscathed from battle. It would be easy to present numerous other instances of tribes and individuals living entirely on a vegetarian diet. It is undeniable that a number of people no fewer than those just mentioned are nourished by animal food exclusively. Certain Africans live upon flesh only. In northern countries, such as Greenland, Lapland and Iceland, where the whole year is harsh and where the soil is almost always frozen under deep snow, fish supply the only source of food. Many witnesses testify that the erstwhile nomadic Scythians, as well as the Tartars of today—truly fierce peoples—have lived on meat alone and still do so. The Patagonians reject bread and greedily gobble down horsemeat.

It is obvious, nevertheless, that man has been designed by nature to be omnivorous. He hunts for almost every kind of food to be found in the sea or on the land. With indiscriminate destructiveness he entices wild beasts from caves and fish from the ocean depths, using them for nourishment. He even seeks food from poisonous sources, which the mind recalls with a shiver and shuns with nausea, and with

great relish he licks down snakes, toads and fungi. The strength of his teeth, adapted to the chewing of either class of food, the structure of his stomach, the presence of gastric juice, the length of the intestinal tract midway between the gut of the herbivorous and of the carnivorous animals, all suggest that man is meant to be omnivorous. The body is enfeebled by deadly disease through the excessive use of a purely vegetable diet. The fibers' strength fails, the limbs grow heavy, spirits ebb, and a kind of dull heaviness oppresses the whole body. Yet the ills arising from the use of meat alone are more severe. The itch, leprosy, dysentery and malignant fevers almost always follow the immoderate use of meat. Those who live on a mixed diet take the best care of their health. We find, therefore, very few persons today who live without cereals. The diet in a warm climate is so adjusted that the vegetable foods predominate considerably, and conversely under a cold sky (D).

Concerning Seasonings

A few words should be said here regarding seasonings which are mixed with most of our foods to make them more pleasing and tasteful, or to retard spoilage. Many of these seasonings are gathered from gardens or from the fields. Some the mineral kingdom provides. Of them all, those in much the most common use are sea salt and sugar. Almost all nationalities mix sea salt with animal food. The eminent Pringle (E) shows by experiment that, used in quantity, it prevents spoilage; purified salt does it the most effectively, as my thrice-repeated experiments demonstrate (3).

Sugar far surpasses all other flavorings. It is rich in nourishment, abounds in antiseptic power, and works against malignant diseases. Pringle (F) advises us that the plague itself is restrained by the generous use of sugar.

We always mingle drink with food. Through countless streams nature generously pours out water for us. The works of Hoffman are brimming with the health-giving characteristics of water. However, its blessings are presented with too much praise. In every age man has longed for drinks more exhilarating and more pleasing to the taste than draughts from the cup of Achelous (4). Men soon gathered grapes ripe on the vines and pressed out their sweet juices. Long ago, also, man discovered the art of brewing beer from grain. Europeans get it from barley, Asians from rice. American savages use, for fermentation, maize mixed with saliva, and draw off from it an intoxicating fluid (5). A sugary reed of the Indes produces a sap from which drinks are made useful for health and strength, at least when taken in moderation. Certain trees exude a very sweet sap, supplying by means of this art an enjoyable spirit (G). The Tartars get an inebriating liquid from horses' milk. In truth, there are people—I shudder to mention them—who lick up the blood of freshly-slain animals and derive their strength therefrom (H).

With these matters out of the way, I now go on to the changes that foods undergo inside the stomach. Thus food, having been thoroughly chewed in the mouth and softened by saliva, is pushed through the esophagus into the stomach where, mixed with a generous supply of saliva and gastric juice, it is made suitable for digestion.

It is quite remarkable that chyle should always result from such diverse foods. This milk-like humor, drawn into small tubes and poured from the thoracic duct into the subclavian vein, by some unexplained power is changed into blood, from which develop all the body's humors in such a wealth of variety.

For bitter bile, mild saliva, salty urine, even prolific semen—all are products of the same food and of the same blood. He who understands the causes of those things shall be in my eyes a mighty Apollo.

Concerning Saliva

Authorities differ as to the contributions of saliva. Some would have it perform the function of water only. The eminent Pringle attributes to it an antiseptic quality and thinks that it performs that function in the stomach (I). Stahl was the first to describe its fermentative power (J). With this opinion Hoffman and

Boerhaave, authors of great repute, are in agreement, but experiments confirming this theory have not yet come to our notice. Saliva undoubtedly possesses a septic power, as will become sufficiently obvious from Experiment V.

Concerning Gastric Juice

It is unfortunate that the gastric juice is so deep within the stomach that it frustrates experimentation. As far as one can surmise, it is a thin fluid of about the same character as that of saliva, for the one often acts as a substitute for the other and we have always found it in generous quantities when, for various reasons, saliva is absent. Hogs discharge a scarcely perceptible saliva, but their glands secreting gastric juice in the stomach are very numerous. On the other hand, in animals almost lacking in gastric glands we always find that they have an abundance of saliva. Grief or other mental experiences can interfere with the digestion of food by disturbing the secretion of gastric juice. Whence it is obvious that the latter's powers are strongly favored by its release (6).

Before going further, the opinions expressed in the past concerning the causes of digestion ought to be summarized briefly. Care must be taken to understand that what is propounded here is relevant only to the nature of the stomach of man. Writers presented a great deal of useless material, while speaking of digestion, when they discoursed as if digestion were the same for every animal. The structure of the teeth and of the stomach differs in each class of animal according to the nature and strength of the food consumed by each one. Then too, the manner of digestion differs in each case. The first matter to be considered, then, is that of trituration.

Trituration

For a long time in the medical schools a mechanical theory of digestion was verbosely maintained. Borelli, Pitcairn (7) and Hecquet (8), trying by mathematical calculation to measure the power of the stomach, took it to be enormous. Pitcairn thinks that its power is equal to 12,951 pounds (9). Other mechanically inclined writers rate its power even higher. Behold! how the mathematicians dream when they attempt to explain the functions of living bodies: from this bubbling spring countless mistakes have flowed into medicine, mistakes over which even now the art of Apollo mourns. The human body enjoys so individual a construction that it refuses subjection to mechanical laws. As a matter of fact, analogies gathered from other areas of nature shed a minimal light on our investigation of animal functions.

Many considerations contradict the theory mentioned above.

First, the power of the stomach, combined with that of the abdominal and diaphragmatic muscles, attains far less strength than that attributed to it by these authors. The eminent Hales, so noted for the Verulamian art (10), found the strength of a recently killed dog's stomach to be 39 pounds. Hence he concluded that the strength of a human stomach never exceeded 20 pounds (K).

Secondly, the membranous lining of the stomach cannot endure such violent treatment, for so great a force would tear apart the fibre-texture and bring with it the most disastrous ailments.

Thirdly, if digestion depended on attrition, all foods would be dissolved over a period of time proportionate to their softness, and the more easily they were dissolved, the more quickly would they become nutritive. But to no one's surprise, experience refutes this opinion, for the softest foods, although often remaining for many hours in the stomach, are unchanged when returned by vomiting.

Fourthly, if the strength of the stomach is as tremendous as mathematical calculation chooses to regard it, will not the manner in which food becomes chyle be more obvious? All foods subject to digestion, after losing the qualities they originally enjoyed, take on new forms. Surely mechanical force is not able to transform the character of foodstuffs in this manner. After the finest possible pulverizing,

there always remains the same mass, raw and undigested.

Solution

Those who base the digestion of food on saliva and gastric juice alone, exaggerate the power of these liquids. They, too, must be contradicted. So, in order that this opinion may be uprooted, aid must be summoned from chemistry. If silver or copper or lead be soaked in aqua fortis, they undergo practically no change and, with the addition of sufficient alkaline salt and the restoration of the inflammable material (11), they recover their original form. Silver never becomes more like lead by this procedure. Neither does copper or lead become similar to silver. It is always this way with the process of dissolution: it causes no lasting change in the characteristics of the dissolved substances. But in the digestion of food there is an obvious transformation not only of form but also of quality, to such an extent that chemical analysis would prove futile in discovering the origins of the foods following digestion.

Putrefaction

Some authorities attribute digestion to putrefaction, to which all kinds of food are naturally subject. It seems to me they are far off the target, for who in his right mind can think that chyle, the mildest of fluids, odorless and sweet, is produced from spoiled food? The stomach has shown no sign of putrid fermentation, and it will be shown quickly that putrefaction does not develop except when the stomach is suffering from disease.

Heat

Galen and many others who obediently follow in his steps attribute digestion of food to heat, but to this notion we object that the temperature of the stomach never goes higher than 98 degrees on Fahrenheit's thermometer (12). Plenty of experiments have been collected to prove this. A temperature higher than that mentioned would immediately cause spoilage of the food elements, and we would look in vain for the naturally sweet chyle from them.

Writers have put forward many other ideas which would take long to review and would be foreign to my own proposal. I now apply myself to other matters that bear more strictly on my subject. Hitherto we have been following nature with a hapless footstep but, coming forth at last from the heavy fogs, the subject finally reveals itself to us in placid simplicity.

Fermentation

The principles of chemistry, transferred for the first time to medicine, captured men's imagination and physiologists wished to adapt all the processes of the human body to chemical laws. From these dreams arose a host of errors regarding the art of medicine. They explained the immediate causes of disease by the powerful influence of salt or by some other perverse defect of the humors. It appears from the light recently thrown on this subject, however, that these oft-repeated defects of the humors were undeservedly reported and condemned, and rightly, therefore, they are dispersed by the art of medicine. Nevertheless, chemical laws, cautiously applied to medicine, are of great assistance, for they aid in correcting mistakes and, as long as they do not trespass due limits, they serve to bring some deeply-buried processes to light.

Van Helmont (L) was the first to suggest the presence of fermentation in the stomach but, in error as to its true cause, he thought that acid was always present as a ferment in the stomach. No experiments appear to establish this belief. It is undeniable that the stomach has an ability to coagulate milk; many things besides acids, however, such as the mucus excreted by the intestine, and even artichoke blossoms, enjoy the same abilities. It is brought out by Experiment I that an acid ferment is not necessarily always present in the stomach.

Three types of fermentation are well-known to all: the vinous, the acid and the putrid. Everyone hesitates, however, to explain the causes upon which this remarkable action of nature depends. So far these causes lie hidden

in shadows and will, perchance, lie so hidden forever.

All types of foodstuffs, whether vegetable or animal, go through these three stages. The first and second always take place in the stomach. For a long time there was disagreement as to whether flesh foods underwent the vinous and acid stages; and because these stages were not evident to the senses, some deny that alcohol or acid can be elicited from it naturally or artificially. The falseness of this idea will be obvious to everyone who follows the arguments to be presented here.

First, all who are knowledgeable in the laws of chemistry or even have an inkling of them know that heat always accompanies fermentation. Chemists of old thought that such heat grew to its maximum in the final stage. Certain recent observations, however, suggest that all heat is dispelled at the onset of putrefaction (M). There are even tests showing that animal matter grows hot while it is being dissolved by fermentation. Cloth-makers offer sad evidence of this fact for, if previously moistened woollen garments be exposed to air, they quickly begin to grow warm and in a short time the anxious fullers, robbed of their hopes, see the garments suddenly consumed by flames. Yet I seem to hear someone contradict this argument. At what stage does heat increase on the manure pile? Isn't there a putrid fermentation present on such a pile? But I deny this for the excrement of horses is full of vegetable juices which pass through the vinous and acid stages before coming to that of putrefaction, and it is only in the former stages that it becomes hot.

Secondly, persons who live for many days on flesh food often taste the expulsion of an acid humor from the stomach. The stomachs of flesh-eating animals emit an acid odor, and chemical analysis reveals an acid humor is excreted in their feces (N).

Thirdly, certain experiments illustrate this question. Beef, preserved for two days in a warm atmosphere, displayed acidity of both taste and odor which was witnessed by a learned gentleman and alumnus of this Academy, the eminent Thomas Smith (13). The eminent Haller, also, gives it credence by saying that he himself noticed the acid odor from heated meat (O). If necessary, it would be easy to summon in support of this opinion many other authorities.

If we consider the nature of food and the phenomena of digestion, we must make the deduction *a priori* that fermentation is always present in the stomach.

First, it cannot be denied that all kinds of animal and vegetable substances ferment, provided they acquire sufficient dissolution, fluidity and air.

(a) Food which is thoroughly broken up in the mouth and shaken about gradually by the motion of the stomach is always broken up to the desirable degree.

(b) The temperature of the stomach is never very far from 98 degrees on Fahrenheit's thermometer. Heat so elevated does not interfere with fermentation, for the higher the heat is raised, the more fermentation flourishes.

(c) Saliva and gastric juice supply the desired fluidity, being poured over the food in large amounts while the usual beverages always taken along with food are added.

(d) Saliva is always full of air and to this is added the air arising from food. Furthermore, the lucid experiments of our own distinguished Professor Black, who burns with true Halesian enthusiasm, serve to support this theory.

Secondly, we must now examine the phenomena of the digestion within the stomach, which seem to agree remarkably well with the phenomena of fermentation. Noticeable in each fermenting mass is a swelling, a release of air, and a total transformation of the fermenting mass. And the digestion of food in the stomach displays all these.

(a) Food, when it enters the stomach, always swells. Everyone testifies to this.

(b) A great quantity of gas is produced from the stomach during the process of digestion, although it becomes obvious only in the case of those suffering from stomach disorder. Van Helmont first gave it the name "gas sylvestris". Does not the desire to sleep, which

we notice after a meal, arise from its narcotic action upon the nerves of the stomach (14)?

(c) When digestion is completed, there occurs an entire transformation in the nature of the food, so much so that chyle differs as much from vegetable nature as from animal nature.

In order to clarify this question, it has seemed best to describe certain experiments involving my own stomach — since it is completely free from any disease — which appear to place this doctrine beyond all doubt.

Experiment I

I dined on beef, peas, bread and beer. Before eating, however, I consumed 5 grains of alkaline salt so that the smallest possible quantity of acid liquid left over from the preceding meal might be suppressed. Three hours after the meal, having taken 2 grains of tartar emetic, I vomited an acid-tasting liquid that turned bright red when sprinkled with an infusion of *Campanula rotundifolia* (15).

Experiment II

Having eaten veal, peas and bread and having drunk only water, I vomited three hours after the meal. The bread, which sometimes has an acidic quality, showed no signs of acidity. As before, I had taken the alkaline salt. The material vomited produced the same red color when sprinkled with the above material.

Experiment III

Having made my meal of hen, cabbage and unleavened bread, I vomited after the usual interval and the fluid thrown off showed the same signs of acidity as before.

Experiment IV

Lest someone object that my stomach is abnormal or affected by some disease, my talented friend, William Penny (16), who has applied himself to studies at this Academy with outstanding success and who enjoys the best of health, vomited after eating duck, beans and bread. The result ran true to form. The fluid vomited had an acid taste and it showed a reddish color when the infusion of campanula was added.

Experiment V

In order to clarify the properties of saliva referred to above, two drams each of lamb and of bread were mixed in two glass vessels. I added one and a half times as much saliva to one, the same amount of water to the other, and placed both in a sand-bath. After five hours, the mixture with saliva began to seethe. After seven hours it showed unmistakable signs of acidity. At the same time, in the mass to which water had been added, practically no motion at all was apparent. After a lapse of twelve hours the mixture with saliva emitted a putrid odor, while the mass mixed with water remained mild and fresh for as long as 20 hours.

This experiment, repeated twice, produced a similarly fortunate result.

So far one knotty problem has not been successfully untangled, i.e. the further transformation of food before it becomes chyle. It seems appropriate to say a little here toward elucidating the question.

Our eminent professor of natural history, Ramsay, in his inaugural dissertation entitled "Concerning Bile", explains that mixing bile with vegetable acid suppresses both their qualities. Experiment XVIII, p. 9: "A mixture, composed of four parts vinegar and five parts fresh bile, produced the taste of neither, but displayed a sort of moderate sweetness."

Experiment XIX. "A mixture of vinegar and bile as made in Experiment XVIII, sprinkled with fresh milk, did not cause the latter's coagulation although the same quantity of acid added by itself would have been more than enough to produce coagulation."

We find the same experiment presented in the book, *On the use, nature and diseases of bile*, written by Baglivi. He points out that after vinegar and bile have been poured together, bitterness is blunted (17). From such experiments the manner in which chyle is produced from food is plain, namely, when the bile is poured into the duodenum. Perhaps bile performs the function of hastening the process by

separating from the food the feces to be eliminated through the common drain of the body (P).

I had intended to add a few words regarding diseases of the stomach, but this would lead me far astray from my original purpose. Allow me to say just a word about the nature and selection of foodstuffs.

Writers grind out much that is worthless and tasteless concerning this subject; an enormous horde of diseases are said to flow from the imprudent intake of food. Since the adaptability of the stomach is so remarkable, the quality of the food matters little. Damage to the stomach is due primarily to the quantity of food consumed. Lucretius has neatly phrased it thus:

It is of no importance by what food the body is nourished, as long as you are able to distribute what you take in to the limbs (18).

Those who learn to live on a little avoid diseases up to an advanced age.

Now I have reached the end of my dissertation into which many unimportant thoughts have found their way. Before laying down my pen, however, I must express my gratitude and warm affection for a man of great learning and a favorite of students, William Cullen, who first suggested to me this subject for investigation and pointed out the right path. Farewell, shining light of the Academy. Your name will be ever in my thoughts, your praises and honors will last forever!

NOTES

1. Jonathan Bayard Smith (1742–1812), Rush's friend, was active for many years in Pennsylvania politics.
2. Jacob Rush (1742–1820) was admitted to the bar in 1769 and later became a judge in Pennsylvania.
3. I have found no other reference to these experiments.
4. "Draughts from the cup of Achelous," i.e., water.
5. *Cf.* Pringle, *op. cit.*, p. xlviii, where this custom is mentioned. Pringle, however, maintains that the action of saliva retards fermentation rather than enhances it.
6. A fertile insight, it is also suggested by Young (*op. cit.*, pp. 20–21) and by William Beaumont (*Experiments and Observations on the Gastric Juice and the Physiology of Digestion* [Plattsburgh, Pa., 1833], p. 87).
7. Archibald Pitcairn (1652–1713), "A Dissertation upon the motion which reduces the aliment in the stomach to a form proper for the supply of the blood," *The Whole Works of Archibald Pitcairn* (2nd edition, London, 1727), pp. 106–138.
8. Phillipe Hecquet (1661–1737), *De la Digestion des Maladies de l'Estomac, suivant le système de la trituration ou du broyment sans l'aide du levain ou de la fermentation* (Paris, 1712).
9. Pitcairn, *op. cit.*, p. 138.
10. I.e., Francis Bacon (1561–1626). Boyle, Hooke, etc., refer to Bacon as "Baron Verulam".
11. This is a reference to the phlogiston doctrine in which heat was considered a material object.
12. The relationship between heat and physiological processes was of great interest in the 18th century and many experiments were conducted. The topic is well reviewed by P. Lorain, *De la Température du Corps Humain, Vol. I* (Paris 1877). The difficulty of interpreting Galen as meaning, literally, elemental fire as a major agent in digestion is discussed by R. P. Multhauf, "J. B. Van Helmont's Reformation of the Galenic Doctrine of Digestion," *Bull. Hist. Med.* **29:** 154–163 (1955).
13. More than one Thomas Smith matriculated at Edinburgh in the 18th century; as of 1768, however, only one Thomas Smith had graduated MD and his thesis of 1767 (*De actione musculari*) was later published in *Thesaurus Medicus, Vol. III* (Edinburgh, 1785), pp. 78–115.
14. This may be one of Rush's original speculations: I have found no earlier suggestion that gas sylvestris is responsible for the sleepiness which occurs after large meals.
15. *Campanula rotundifolia*, the bluebell, was in Scottish folklore regarded with a sort of dread and commonly was left unpulled (James Britten and Robert Holland, *A Dictionary of English Plant Names* [London, 1886], p. 507).
16. William Penny took the degree of MD at Edinburgh in 1769, the subject of his thesis being *De motu febrium periodico*. He described himself as "Britannicus", which may mean that he was Scottish rather than English.
17. Georgio Baglivi (1668–1707), *Opera Omnia, Medico-practica et Anatomica* (Venice, 1752), pp. 251–252 ("De experimentis circa bilem, ejusdem natura, usu et morbis").
18. Lucretius, *De rerum natura*, Book IV, ll. 630–632. Rush quotes the unbracketed portion of the text: nec refert quicquam quo victu corpus alatur, dummodo quod capia[s concoctum] didere possis artubus [et stomachi umidulum servare tenorem.]

Dr. Jules L. Prevost and the Teaching of Medical History at Temple University School of Medicine, 1910-1965[1]

By FRED B. ROGERS, M.D.[2]

TEMPLE University School of Medicine, youngest of Philadelphia's five medical schools, opened in the year 1901. From humble beginnings the school has made bold progress, in large part because of its fine faculty. Though relatively young in years, in one particular teaching area, that of providing continuous instruction in medical history for its students, Temple has a long tradition. Dr. Jules L. Prevost in 1910 began the course in History of Medicine which continues to this day. An Episcopal missionary to Alaska before receiving his M.D. degree, Prevost remained primarily a clergyman. Because he was not a professional medical historian who could devote time to scholarly research, Dr. Prevost did not achieve more than local reputation in this field. His remarkable clerical career and pioneer service in our 49th state, however, in addition to the teaching of medical history and terminology, make his life and work deserving of recall.

Jules Louis Prevost was born on June 20, 1863, at Brooklyn, New York, of Huguenot descent. Little is known of his parents; his mother died shortly after his birth and his father soon after her. The boy's childhood was austere; from infancy to his teens he lived at the Leake and Watts Orphan House in Brooklyn. A relative, Mrs. Susan Chambettaz, whom he called "Aunt Susan", had charge of his adolescent years. At St. Michael's Church, New York City, where Jules sang in the choir and was confirmed at age fourteen, he met two clergymen, the Rev. Dr. Thomas M. Peters and the Rev. Dr. John P. Peters, father and son, who influenced his decision to enter the ministry.

Prevost's early education was obtained in Brooklyn public schools and at an academy in Plainfield, N. J. About 1880 he signed aboard a sailing ship as mess boy, living at sea for a period of two years and visiting Spain and Portugal during this interval. Schooled by books as well as travel, he received a teacher's certificate, 2nd class, from the Board of Instruction, Nassau County, Florida, on September 15, 1882, and taught at Public School No. 42 at Oak Grove and then in a school at Callahan, Duval County, Florida.

Returning to New York City in 1885, Prevost spent two years as entry clerk at the Roosevelt Hospital, learning much that would help him in future years. In 1887 he left to study for the ministry, entering the Philadelphia Divinity School where his former pastor, the Rev. Dr. John P. Peters, was Professor of Old Testament languages and literature and at the same time Professor of Hebrew at the University of Pennsylvania. Jules Prevost received his Bachelor of Divinity degree on May 28, 1890, and was ordained Deacon by Bishop Whitaker of Pennsylvania in the following month.

Intending to do missionary work in Algeria, Prevost studied Arabic at the University of Pennsylvania (1887-1888), but an appeal by William Duncan of the "Indian Rights Society" on behalf of Alaskan Indians and their needs turned him in that direction. The summer of 1890 was spent investigating and re-

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FIG. 1. The Rev. Jules L. Prevost, M.D. (1863–1937). Photograph by Gutekunst of Philadelphia.

porting on the living conditions of Indians in Southeast Alaska.

Returning to Philadelphia Prevost matriculated in the medical school of the University of Pennsylvania, with the objective of obtaining a degree that would be of benefit in missionary work. (Continuing this interest, he served as chaplain of the Indian Home in Germantown during 1890–91.)

Answering a call to relieve an English missionary in Alaska, Prevost dropped his medical studies, was ordained Priest in the Chapel of the Philadelphia Divinity School on April 29, 1891, and left a week later for St. James Mission at Fort Adams on the Yukon River. Travelling via San Francisco, he arrived at the remote Alaskan outpost on August 1, 1891.

Fort Adams, a trading station founded in 1874, was situated eighteen miles below the point where the Tanana River enters the Yukon. During the winter of 1892 Mr. Prevost made a trip up the Tanana River, far beyond where, ten years later, Fairbanks was built, and crossed to Forty-Mile River and the town of that name where he started a library for the miners. Retracing this route the following year, he journeyed 500 miles upstream to Lake Mansfield and visited thirty-two Indian villages in this vast area.

A small printing press was sent to the St. James Mission by friends in the United States in the spring of 1892. Using this device Prevost printed the first newspaper in the interior of Alaska, the "Yukon Press" (vol. 1, no. 1, Jan. 1, 1893)—a periodical carrying regional news. This newspaper prospered until 1897 when the printing outfit was moved to Circle

FIG. 2. Map of Alaska, showing the Yukon River Basin and other sites served by Dr. Prevost. (From: James Wickersham: *Old Yukon: Tales—Trails—and Trials*, Washington, D. C., 1938.)

City. (Rescued from a refuse heap over twenty years later, the historic press was donated to the Alaska Agricultural College at Fairbanks where it can be seen today.)

A book, *Old Yukon: Tales—Trails—and Trials*, by Judge James Wickersham of Juneau (1938), tells of Mr. Prevost's varied activities in Alaska:

> Besides getting out the paper, Prevost performed the duties of preacher, physician, midwife, undertaker, woodcutter, berrypicker, distributor of second-hand clothes to his Indians, watercarrier, fisherman and dogdriver. . . .
>
> In the summer of 1894, he wrote, translated, set the type, and printed the first book issued from any press on the northwest coast of North America, north of Juneau, Alaska. Its title is "Tennatla bu Chilichu Christtsun", and freely translated it means, "Tena Book of Songs to Christ". It was printed at "Fort Adams, St. James Mission, 1894, 16 pages, by Archdeacon T. H. Canham and Jules L. Prevost." These collaborators lived, one at Fort Selkirk, and the other at Fort Adams, some 800 miles apart.

Prevost mastered the Tena tongue and its Qliyikuwhutana dialect, compiled a vocabulary of the Athabascan languages, and translated portions of the Book of Common Prayer for use by the Indians. Describing them he said: "They are a really loveable people, industrious, frank, teachable and too susceptible, if anything, to the customs and manners of civilization." Living in a wilderness with Indians, miners, trappers and traders brought daily problems. A tribute to Prevost in *The Alaskan Churchman* (1906) noted: "His Christianity was of the muscular school; white man leading native astray has more than once felt the weight of his fist, and native whom he caught drinking down town has often been dragged up the trail by the scruff of the neck and kept in durance until sober."

Returning on furlough to the United States in the fall of 1894, Jules Prevost married his long-time sweetheart, Anna Louise Demonet, in Brooklyn. During this visit to the States, he took the senior year of study at the New York School of Pharmacy.

In 1895 Mr. Prevost and his bride went out

to Fort Adams on the Yukon. During the following year, due to shoaling of the river, the church was moved twelve miles distant to the trading station of Tanana. Here a hospital and a school were also constructed. A small steamboat, the "Northern Light", built especially for the missionary, became the first such craft to ply the Tanana River.

A son, Horace Cecil, was born to the Prevosts at Tanana on July 13, 1896. In the next year, Mrs. Prevost's mother came to Alaska from Brooklyn to be with them. Later the family moved to Circle City, a booming mining camp, where a mission and hospital were founded. In 1897 a daughter joined the family circle.

On July 5, 1898, Prevost was appointed first postmaster of Tanana by Postmaster General Charles Emory Smith. After returning there, Mrs. Prevost, her mother and children being in poor health, they began the long trip back to New York. On the way down the Yukon, the daughter died and her body was sent back to her father at Tanana for burial.

In the next year, 1900, Mr. Prevost joined his family in Brooklyn on a fund-raising leave for the Alaskan missions. He returned to Tanana in 1901; his wife joined him two years later and remained until 1906. During this period two more sons, Jules Faure and Percy Vaucher, were born.

During his fifteen years in the Alaskan field, Prevost had founded missions at Circle and Rampart on the Yukon; Nome and Valdez on the coast. Rampart, farther down the Yukon, grew up in 1898. Prevost spent the next winter there and built a small hospital and chapel in the town. Nome had been a deserted spot on the Seward Peninsula until gold was discovered in its sands later in 1899. It mushroomed almost overnight from the rush to this 'strike'. Journeying overland from Rampart by horse and dog sled with six companions at the request of his Bishop, Prevost travelled forty-four days over the Yukon trail to Nome. (The missionary, in April, 1900, rode the first horse into the city of Nome.) Selling everything he could, including his 'grub outfit' and typewriter, he bought two lots and staked a tent for church services. Valdez, located on Prince William Sound, developed as a port for copper mines. Prevost stopped there in August 1900, on his way out on furlough after his stay at Nome. He organized a congregation and supervised the construction of a rough building for use as a chapel. Early in 1906, before leaving Alaska permanently, Prevost attended the consecration of the Church of Our Saviour at Tanana—a native chapel made possible through his labors and the generosity of Miss Mary Rhinelander King of New York.

In the year 1907, after his permanent return to the United States, Mr. Prevost accepted charge of St. Ambrose's Church in Philadelphia, where he remained for three years. During this period he studied medicine at Temple University, receiving an M.D. degree on June 5, 1909. While a medical student he was a member of the Babcock Surgical Society, Applegate Obstetrical Society and Krusen Gynecological Society, and served as chaplain of Omega Epsilon Lambda fraternity.

Dr. Prevost graduated in medicine at the age of 46. It was a second calling to him, and, except for helping Dr. Robert B. Carey of Glen Loch during the influenza epidemic in 1918–19, he did not attend patients. He felt that medical knowledge helped his understanding of people, their problems and needs.

Because of special interest, Dr. Prevost was appointed Lecturer on History of Medicine and Medical Terminology at Temple University School of Medicine by letter of November 15, 1909, signed by Dr. John E. Rommel, Assistant to the Dean. The *Bulletin* of Temple Medical School for June 1910 lists Prevost in the above capacity under 'Theory and Practice of Medicine' and states: "The history of medicine and medical terminology are covered during the freshman year." A full course of lectures was initiated in the Fall of 1910. The medical school catalog for 1911–12 described it thus:

> One lecture is given weekly for the first half of the session on the history of medicine. In the second half of the session medical terms are defined etymologically

and often historically, and their practical application outlined. A final examination is held at the end of the session.

For eighteen years, from 1910 to 1929, Dr. Prevost presented this introductory course—a survey based on standard textbooks. After sixteen years the medical terminology portion was dropped from the curriculum. The school's catalog for 1927–28 records under 'History of Medicine: First Year', "One lecture is given weekly during half the session."

Recollections by several of Prevost's former students are interesting and amusing: "Dr. Prevost was a cheerful, hearty man, more priest than physician—he wore gaiters like the country parson that he was." . . ."He knew more about dead and modern languages than his pupils did." . . ."His talks were instructive, but the course was a minor one so we didn't take it seriously." . . ."He gave a simple quiz and, being obsessed with anatomy, chemistry, and physiology, I don't recall much of what he said." At least one of Prevost's students, Dr. Reuben Friedman (1892–1956), Class of 1916, became a notable medical historian.

Years close to nature in Alaska turned Jules Prevost away from city life. A son's delicate health and a wish that his children enjoy the advantages of rural life motivated a return to the country. Therefore, in 1910, he left St. Ambrose's Church, where a grateful men's class erected a tablet to him, and accepted the charges of St. Paul's Church, West Whiteland (Glen Loch) and St. Peter's Church in the Great Valley, Chester County. A book, *The Church of Saint Peter in the Great Valley, 1700–1940*, by Harold E. Eberlein and Cortlandt V. D. Hubbard, records that late in 1909:

> The Vestries of St. Peter's and St. Paul's united in calling to the joint rectorship the Venerable Jules Louis Prevost, M.D., sometime Archdeacon of Alaska. Dr. Prevost accepted the call and entered upon his duties as Rector of the two parishes in the spring of 1910. Dr. Prevost's rectorship lasted until 1924 and was a blessing to both parishes, to whose people he greatly endeared himself. It was a period of steady growth at both St. Peter's and St. Paul's and there was marked progress, both temporal and spiritual. In conjunction with his parochial duties Dr. Prevost carried on missionary work among the Italian quarrymen and their families in the nearby village of Cedar Hollow and also in other places.

In 1913 the Rector, who was greatly interested in the history of his churches, proposed an Annual Day, to be held at St. Peter's, uniting parishioners and friends through an Association to preserve the country parishes and extend their outreach. Dr. Prevost was president of this Association until 1936. The church history continues:

> In 1925, much to the regret of the Vestry and congregation, Dr. Prevost resigned the rectorship of St. Peter's in order 'to take up other work at the request of the Bishop.' He nevertheless retained his affection for St. Peter's and a deep concern for the welfare of the parish, continuing to officiate there whenever circumstances permitted and remaining Rector Emeritus until his death in September 1937.

In 1918, at the start of The Church Farm School, surrounding St. Paul's Church, Dr. Prevost became instructor in French, Hygiene and Religious Education, and he taught these subjects for seven years. While at Glen Loch he attended several rural conferences at Pennsylvania State College, served on the local school board, and helped to develop the National Grange Organization in the Great Valley. Dr. Prevost's wife died on September 2, 1919; a memorial was dedicated to her memory at St. Paul's Church.

In 1925, at the request of Bishop Taitt of Pennsylvania, Dr. Prevost took charge of the Bucks County Mission of the Episcopal Church with headquarters at Langhorne. In this capacity he attended the Rural Church Summer School at the University of Wisconsin in the following year.

Dr. Prevost was remarried at Philadelphia on December 14, 1928 to a family friend, Ethel R. Patterson. In the following year he accepted a call to St. Andrew's Church, Panama City, Florida, where he remained until Easter of 1933. While in Florida he was active on the local school board and was a charter member of the Kiwanis Club.

Dr. Prevost's resignation from the faculty of Temple University Medical School was

occasioned by his move to Florida. Dean Frank C. Hammond and Dr. William Egbert Robertson, Professor of Medicine, wrote letters expressing the gratitude of the school for his good service.

Returning to Pennsylvania near the age of pastoral retirement in 1933, Dr. Prevost assumed temporary charge of The Washington Memorial Chapel at Valley Forge upon the death of its founder, The Rev. W. Hubert Burk, who had been a seminary classmate. Prevost continued in this ministry until six months before death from heart disease at his home at Pughtown on September 2, 1937. Burial was in the cemetery at the Valley Forge Chapel.

EPILOGUE

Following Dr. Prevost's departure from Temple University School of Medicine, Dean William N. Parkinson and Dr. Robertson invited Dr. Victor Robinson of New York City, eminent author, editor and lecturer, to join the faculty as Professor of the History of Medicine. A full-time worker in this field, he began teaching at the medical school in the fall of 1929. During his tenure the scope of instruction in medical history was expanded and became an integral part of the medical student's total experience.

Dr. Robinson's career has been well reviewed in published accounts. Born in the Ukraine on August 16, 1886, the son of a physician, he came to the United States with his parents when three years old. A graduate in pharmacy from the New York College of Pharmacy (1910), which Dr. Prevost had earlier attended, Victor Robinson also studied at the New York University Law School and at Columbia University. He received an M.D. degree in 1917, at age thirty-one, from the Chicago College of Medicine and Surgery (now Loyola University Medical School) but, like Prevost, did not practice medicine. Dr. Robinson was, to use Dr. George Rosen's phrase, "a romantic medical historian". He stimulated students at Temple University for seventeen years, presenting the history of medicine each year in fifteen hourly lectures. Covering the whole range of medical history, from primitive to modern times, he also included an hour on art, satire and caricature in medicine. An erudite and witty speaker, he amazed and amused his classes by vivid lectures dramatically delivered and illustrated by choice lantern slides. The latter often came from photographs he had taken on visits to historic sites abroad.[3] His outlook and his reputation were international.

Victor Robinson taught the first-year course in History of Medicine to medical students from 1929 through 1946, and lectured on History of Nursing to student nurses from Temple, Episcopal, Germantown and Jewish Hospitals from 1937 until his death on January 9, 1947. It is said that no student ever cut or slept through his classes!

Ten years after his death, in 1957, an annual Victor Robinson Lecture in History of Medicine was established at Temple University School of Medicine. Dr. George Rosen of Columbia University inaugurated this lectureship in 1958 and Dr. Lloyd G. Stevenson of Yale University presented the lecture for 1964. A portrait of Dr. Robinson, painted by Mr. Neil Kosh of Temple's Tyler School of Art, hangs in the medical school auditorium. (Fig. 3) It depicts Victor Robinson beside several of his well-known books: *Pathfinders in Medicine*, *The Story of Medicine*, *White Caps: The Story of Nursing*, *Victory Over Pain: A History of Anesthesia*. (The last-named book was one of twenty-six titles on medicine and public health chosen for inclusion in the White House Library by Mr. James T. Babb, Librarian of Yale University and his Committee in 1963.)

From 1948–54 inclusive, a yearly series of lectures on medical history was presented at The College of Physicians of Philadelphia for students from all the Philadelphia medical schools. The lectures were given by Drs. Richard A. Shryock and Owsei Temkin of The Johns Hopkins University. In the spring of

[3] Dr. Robinson's collection of lantern slides is now in The National Library of Medicine, Bethesda, Maryland.

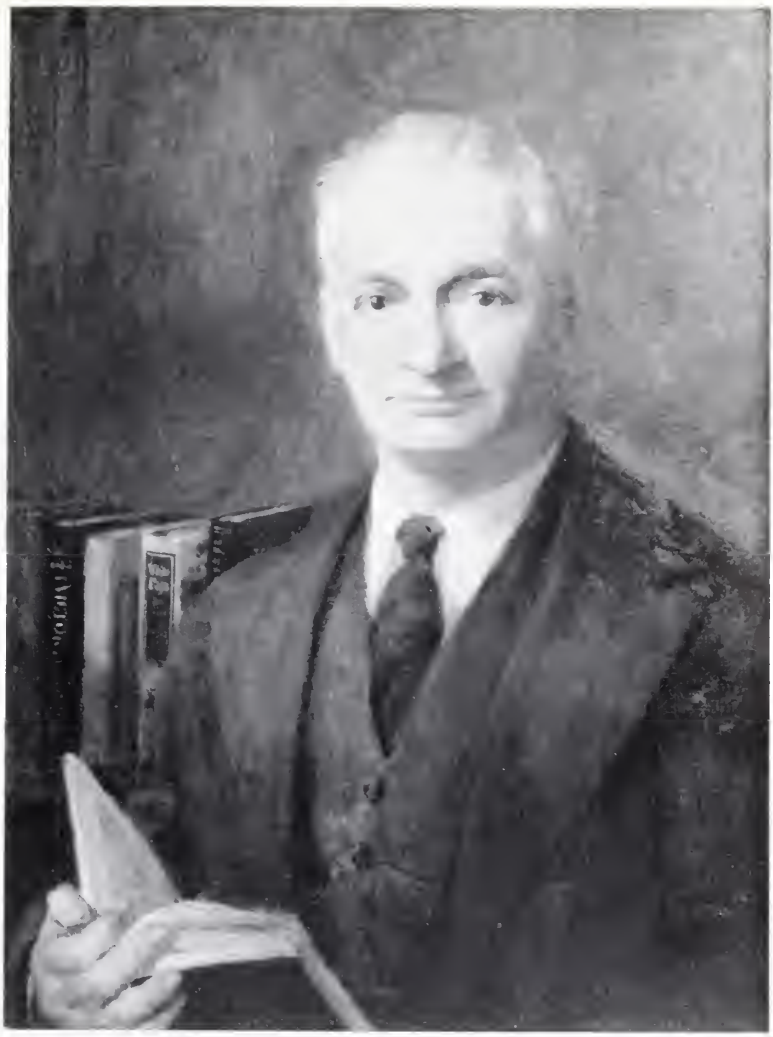

FIG. 3. Victor Robinson, M.D. (1886–1947). Portrait by Neil Kosh at Temple University School of Medicine.

1955 these two eminent medical historians conducted several seminars designed to encourage the schools to institute their own courses in the subject. Temple's representative was Dr. Fred B. Rogers, a former student of Dr. Robinson. Since the fall of 1955 Dr. Rogers has taught the course in History of Medicine at Temple University. A weekly lecture is given, plus a field trip to the Library and Museum of The College of Physicians of Philadelphia. A printed *Syllabus* is used, a final examination held, and a grade recorded for each student.

For fifty-five years, a course in medical history, a brief but significant one initiated by Dr. Prevost, has been presented to Temple medical students. By adding a cultural dimension to the technical curriculum, it has aided the transition from premedical to medical studies and instilled in them an awareness of the background of their profession.

ACKNOWLEDGMENTS

I thank the following persons for their aid in providing unpublished and published material,

documents and photographs of biographical interest: Mrs. Jules L. Prevost, Chester Springs, Pa.; Mr. Percy V. Prevost, Panama City, Fla.; Mr. William W. Manross, Librarian, The Divinity School of the Protestant Episcopal Church in Philadelphia; Miss Jane K. Mees, Overseas Department, Episcopal Church Center, New York City; Mrs. M. Jane Bird, University of Pennsylvania Archives; Miss Marianne Lynch, Curator of Templana, Temple University Library; The Rev. Dr. Walter E. Frieman, Jr., St. Ambrose's Church, Philadelphia; The Rev. Frederick A. Breuninger, St. Peter's Church in the Great Valley; Mr. Charles W. Schreiner, Jr., Headmaster, The Church Farm School, Paoli, Pa.; The Rev. Dr. John Robbins Hart, The Washington Memorial Chapel, Valley Forge, Pa.; Mrs. Ellen H. Ringer, Fort Pierce Beach, Fla.

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Transactions of the Sections

SECTION ON GENERAL MEDICINE

22 February 1965

METASTATIC MALIGNANT MELANOMA FROM MOTHER TO FETUS. Isadore Brodsky, M.D.*, Martin Baren, M.D.*, S. Benham Kahn, M.D.*, George C. Lewis, Jr., M.D., and Milton Tellem, M.D.* (Discusser: J. Wayne Streiten, M.D.*) (*Abstract 1, below*)

METHYLMALONATE EXCRETION IN VITAMIN B_{12} DEFICIENCY. S. Benham Kahn, M.D.*, William J. Williams, M.D., and Lewis A. Barness, M.D.* (Discusser: Lewis A. Barness, M.D.*) (*Abstract 2, below*)

CARBON MONOXIDE PRODUCTION AS AN INDEX OF HEMOGLOBIN DEGRADATION. Peter White, M.D.*, Ronald F. Coburn, M.D.*, Manfred I. Goldwein, M.D.*, and William J. Williams, M.D. (Discusser: William J. Williams, M.D.) (*Abstract 3, below*)

COMBINED VINBLASTIN AND CHLORAMBUCIL THERAPY OF HODGKIN'S DISEASE. John R. Durant, M.D.* (Discusser: Manfred I. Goldwein, M.D.*) (*Abstract 4, below*)

22 March 1965

"THE DIFFICULT PATIENT". Herman Hirsh, M.D.*, and William A. Steiger, M.D. (Discusser: John H. Nodine, M.D.*) (*Abstract 5, below*)

DEPRESSIVE REACTION IN INTERNAL MEDICINE. Joseph W. Slap, M.D.*, and John H. Nodine, M.D. (Discusser: Paul J. Poinsard, M.D.) (*Abstract 6, below*)

BEHAVIORAL REACTIONS TO SURGICAL PROCEDURES. Floyd S. Cornelison, Jr., M.D.* (Discusser: Charles C. Wolferth, Jr., M.D.) (*Abstract 7, below*)

ILLNESS AS A WAY OF LIFE. J. Elizabeth Jeffress, M.D.* (Discusser: Van Buren Osler Hammett, M.D.) (*Abstract 8, below*)

26 April 1965

HYPERGLYCERIDEMIA AND ATHEROSCLEROSIS. Peter T. Quo, M.D.* (Discusser: William L. Holmes, PH.D.*) (*Abstract 9, below*)

LONG-TERM EFFECT OF HEPARIN ON FAT TOLERANCE TESTS. Asher Waldow, M.D.* (Discusser: Harry Goldberg, M.D.) (*Abstract 10, below*)

ISOLATION AND QUANTITATION OF PLASMA SEX HORMONES IN PATIENTS WITH CORONARY ARTERY DISEASE. Henry S. Kroman, PH.D.*, Sheldon R. Bender, M.D.*, and Alfred N. Brest, M.D.* (Discusser: Sheldon R. Bender, M.D.*) (*Abstract 11, below*)

CURRENT CONCEPTS OF THE TREATMENT OF HYPERLIPIDEMIA. William L. Holmes, PH.D.* (Discusser: Peter T. Quo, M.D.*) (*Abstract 12, below*)

SECTION ON MEDICAL HISTORY

(During the academic year 1964–65, as part of the Bicentennial of Medical Education, the Section devoted one program to each of Philadelphia's five medical schools.)

9 March 1965

PROGRAM ARRANGED BY HAHNEMANN MEDICAL COLLEGE AND HOSPITAL.

FELICE FONTANA (1730–1805): A FORGOTTEN PHYSIOLOGIST. Joseph R. DiPalma, M.D.

JOHN HUNTER (1728–1793): CREATIVE SURGEON. Bernard L. Segal, M.D.

CONTRIBUTIONS BY WILHELM HIS, JR., AND MAX FREUDWEILER ON THE PATHOGENESIS OF ACUTE GOUT. Joseph M. Brill, M.D., and Daniel J. McCarty, M.D.

13 April 1965

PROGRAM ARRANGED BY TEMPLE UNIVERSITY SCHOOL OF MEDICINE.

DR. JULES L. PREVOST AND THE TEACHING OF MEDICAL HISTORY AT TEMPLE UNIVERSITY SCHOOL OF MEDICINE, 1910–1965. Fred B. Rogers, M.D.

* By invitation.

Dr. Henry Wirz and Andersonville Prison: A Matter of Justice. H. Taylor Caswell, M.D.

Dr. Paul-Ferdinand Gachet: Vincent Van Gogh's Last Physician. Remo Fabbri, Jr., M.D.

Presentation of Edward Bell Krumbhaar Prize in Medical History (VI) to Ronald E. Rossman, A.B., Senior Medical Student, University of Pennsylvania School of Medicine.

SECTION ON OPHTHALMOLOGY[1]

18 February 1965

Nutritional Retrobulbar Neuritis—A 30 Year Study. Frank D. Carroll, M.D.* Assistant Clinical Professor of Ophthalmology, Columbia University, College of Physicians and Surgeons.

18 March 1965

Basal Cell Carcinoma of Eyelids and Treatment. David B. Soll, M.D. (Discusser: John S. McGavic, M.D.)

The Repair of Vertical Lid Lacerations and Secondary Surgery for Vertical lid Cicatrices. Edmund B. Spaeth, M.D. (Discusser: Gerard M. Shannon, M.D.)

15 April 1965

The Clinical Applications of Ultrasonography. Richard E. Goldberg, M.D.* (Discusser: Lov K. Sarin, M.D.*)

Bilateral Superior Oblique Tenectomy for the A Pattern in Strabismus. E. Howard Bedrossian, M.D. (Discusser: William E. Krewson, 3rd, M.D.)

SECTION ON OTOLARYNGOLOGY[2]

17 March 1965

(Combined meeting in New York City, Section on Otolaryngology, The New York Academy of Medicine, and Section on Otolaryngology, The College of Physicians of Philadelphia.)

Special Award of Merit to Samuel Rosen M.D., Presented by Joseph L. Goldman, M.D.

Hearing Loss and Coronary Heart Disease. Samuel Rosen, M.D. (Discussers: Joseph Sataloff, M.D., and Seymour H. Rinzler, M.D.)

Acoustic Tumor Surgery. William F. House, M.D. (Discussers: John L. Pool, M.D., and Frederick Harbert, M.D.)

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

6 May 1965

Careers in Epidemiology. Alexander D. Langmuir, M.D.*, Chief, Epidemiology Branch, Communicable Disease Center, U.. S. Public Health Service, Atlanta, Georgia. (Sponsored by the Department of Preventive Medicine, Woman's Medical College of Pennsylvania.)

25 May 1965

(Joint Meeting with Pennsylvania Public Health Association, Region One.)

Community Mental Health Programs in Britain and the United States. Michael B. Shimkin, M.D., Henry R. Rollin, M.D., D.P.M.*, R. Bruce Sloane, M.D., D.P.M.*, and William A. Steiger, M.D.

ABSTRACTS

Abstract 1

Metastatic Malignant Melanoma from Mother to Fetus. Isadore Brodsky, M.D., Martin Baren, M.D., S. Benham Kahn, M.D., George C. Lewis, Jr., M.D., and Milton Tellem, M.D. Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

The second case of metastatic melanoma from mother to placenta and infant is presented. The primary tumor was removed from the mother three years prior to delivery. A metastatic nodule was noted on the abdomen by the

* By invitation.

[1] Abstracts of the presentations at this Section customarily appear in the *American Journal of Ophthalmology* and *A.M.A. Archives of Ophthalmology*.

[2] Abstracts of the presentations at this Section customarily appear in the *A.M.A. Archives of Otolaryngology*.

mother two weeks after the last normal menstrual period. During pregnancy multiple nodules appeared over the entire body. Cesarean section was performed at term with delivery of a 7 pound, 13 ounce male infant. Seventeen days after the delivery the mother expired from disseminated metastatic melanoma.

At birth, tumor cells were noted in the umbilical cord blood, and the infant had an unusual hematologic picture characterized by a mild anemia, macrocytosis, normoblastosis, thrombocytopenia, leukopenia and agranulocytosis. The abnormal hematologic state was related in part to folic acid deficiency in both the mother and infant. A pigmented lesion was noted on the anterior chest wall on the eleventh day of life. Biopsy revealed malignant melanoma. Many new lesions developed and the infant expired 48 days after birth from disseminated melanomatosis. An unsuccessful attempt was made to overcome the infant's tolerance to the maternal melanoma cells by maternal grandmother's skin homografts. Theories regarding the acceptance of maternal tumor cells by the fetus in utero are reviewed.

Abstract 2

METHYLMALONATE EXCRETION IN VITAMIN B_{12} DEFICIENCY. S. Benham Kahn, M.D.†, William J. Williams, M.D., and Lewis A. Barness, M.D., Departments of Medicine and Pediatrics, University of Pennsylvania School of Medicine, and Hematology Section of Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Methylmalonic acid (MMA) is an intermediary metabolite in the conversion of propionate to succinate. In biological systems the following reactions have been shown to occur: (1, 2)

(1) Propionic acid + ATP + CoA $\xrightarrow{\text{Act. Enz.}}$ propionyl CoA + AMP + PP.

(2) Propionyl CoA + CO_2 + ATP $\underset{\longleftarrow}{\xrightarrow{\text{Biotin}}}$ methylmalonyl CoA + ADP + P.

† Present address: Hahnemann Medical College and Hospital, Philadelphia, Pa.

(3) Methylmalonyl CoA $\underset{\longleftarrow}{\xrightarrow{\text{Vit. } B_{12} \text{ Co-enzyme}}}$ Succinyl CoA.

In experimental animals deficient in vitamin B_{12}, MMA is excreted in the urine. Recently MMA excretion has also been found in humans deficient in vitamin B_{12} (3, 4). We have studied 12 patients with vitamin B_{12} deficiency in an attempt to correlate MMA excretion with clinical and laboratory signs of vitamin B_{12} deficiency, and to determine the response of MMA excretion to therapy with vitamin B_{12}. MMA was determined by two-dimensional paper chromatography. With this procedure no MMA is detected in the urine of normal human beings or in disease states not associated with vitamin B_{12} deficiency.

The twelve patients studied had vitamin B_{12} deficiency as demonstrated by typical clinical and hematologic findings, low serum vitamin B_{12} levels or both. All excreted MMA in the urine, and this disappeared after appropriate vitamin B_{12} therapy in all. Throughout the pre- and post-treatment periods of the study, clinical and hematologic findings and the effect of therapy were related to the excretion of MMA in each patient.

The results may be summarized as follows:

(1) There was no correlation between the initial hemoglobin concentration and the initial MMA excretion.

(2) There was no correlation between neurologic signs of vitamin B_{12} deficiency and the excretion of MMA.

(3) Administration of sodium propionate failed to increase MMA excretion, suggesting that MMA excretion in man may arise from sources other than propionate.

(4) During vitamin B_{12} replacement therapy the time for complete disappearance of MMA was variable and was not well correlated with the amount initially excreted. In one patient who excreted 31 mgm. per day, and in another who excreted 1.4 mgm. per day, a single 1,000 μg. injection of vitamin B_{12} abolished MMA excretion rapidly. In a group of 3 patients being treated with injections of 100 μg. of vitamin B_{12} daily, MMA excretion was abolished in one in less than 5 days, in the second

in 9 days, and in the third in greater than 10 days.

(5) In four vitamin B_{12} deficient patients undergoing replacement therapy with vitamin B_{12}, MMA was detected in the urine at a time when the clinical and hematologic picture as well as the serum vitamin B_{12} activity was normal. Continued vitamin B_{12} therapy was necessary to abolish MMA excretion.

These data indicate that MMA excretion is a more sensitive indicator of vitamin B_{12} deficiency than is the serum vitamin B_{12} activity, and suggest that the use of MMA excretion as a screening test for vitamin B_{12} deficiency will detect more patients with vitamin B_{12} deficiency than will the serum vitamin B_{12} activity.

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Abstract 3

Carbon Monoxide Production as an Index of Hemoglobin Degradation. Peter White, M.D., Ronald F. Coburn, M.D., Manfred I. Goldwein, M.D., and William J. Williams, M.D., Hospital of the University of Pennsylvania, Philadelphia, Pa.

Since the original isotope studies of bile pigment metabolism by London (1) and by Gray (2) and their groups, it has been known that normally 10–20% of fecal bile pigment does not arise from the degradation of hemoglobin at the end of the red blood cell life span, but rather appears as a so-called "early-labelled peak" within the first few days after isotope administration, before circulating erythrocytes show comparable labelling of their hemoglobin. In certain hematologic disorders, notably pernicious anemia, thalassemia, and primary refractory anemias, this early peak is grossly exaggerated and stercobilin production may be significantly in excess of values attributable to circulating heme turnover. This picture of high stercobilin excretion, accompanied by a hyperplastic marrow, high serum iron turnover, poor incorporation of iron into circulating hemoglobin, and relatively minor shortening of circulating erythrocyte life span, has been termed "ineffective erythropoiesis" (3).

We have studied three such patients, one with thalassemia and two with primary refractory anemia, with particular reference to their endogenous carbon monoxide production. Previous studies by Coburn *et al.* (4) have shown that carbon monoxide is an end product of normal human metabolism. Experiments in humans and dogs have indicated that CO arises from the alpha-methane bridge carbon atom of heme, and data obtained in normal adults and in patients with hemolytic anemia indicate that 75–80% of endogenous CO in these subjects can be attributed to the catabolism of hemoglobin of senescent red blood cells, findings which are in agreement with previous knowledge of bile pigment metabolism.

In contrast, the present group of patients with ineffective erythropoiesis were shown to have CO production rates considerably in excess of turnover rates of circulating heme. Isotope studies with glycine-2-C^{14} demonstrated exaggerated "early-labelled peaks" of stercobilin in these patients. By washing out body carbon monoxide stores under high partial pressure of oxygen, followed by selective trapping of the CO, it was possible to show that the "early-labelled" stercobilin peak was accompanied by an "early-labelled" carbon monoxide peak which would also appear to arise from sources other than circulating hemoglobin. A normal subject given glycine-2-C^{14} also showed an early $C^{14}O$ peak concomitantly with the normal early C^{14}-sterco-

bilin peak, followed by the reappearance of labelled CO and labelled stercobilin at the end of the erythrocyte life span.

The parallelism between CO production and stercobilin production suggests that measurement of carbon monoxide production rates may provide a useful index of hemoglobin degradation in the presence of a variety of hematopoietic disorders.

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Abstract 4

Combined Vinblastin and Chlorambucil Therapy of Hodgkin's Disease. John R. Durant, M.D. Department of Medicine, Temple University School of Medicine, Philadelphia, Pa.

Sixteen patients with active disseminated Hodgkin's Disease were treated with a combination of intravenous Velban (vinblastin) and oral chlorambucil. Dosages of these agents were adjusted to provide the maximum response or the absence of a response with a white blood cell count of less than 4,000. The average dose of vinca leukoblastin required to produce this was 0.06 mg./kg./week. Thus a hypothetical 70 kg. patient would receive 8.4 mg. of vinblastin every other week and an average of 5 mg. chlorambucil a day.

Thirteen of the 16 patients fulfilled Karnofsky's criteria for IA response. Six of the patients were considered to have an excellent, that is, a complete response, and seven of the patients a good response. The duration of the remissions ranged from 2–12 months with an average of 7½ months; however, six of the responders were in remission at the time of the report, thus indicating that the true length would be longer than the stated 7½ months. Toxicity encountered was minimal and no patient had to be admitted to the hospital because of it.

The data presented indicates that a combination of low dosage vinblastin and chlorambucil in Hodgkin's Disease can produce an excellent response for a significant duration with low toxicity. There may be a synergism between these agents.

Abstract 5

"The Difficult Patient". Herman Hirsh, M.D., and William A. Steiger, M.D. Department of Community Medicine, Temple University School of Medicine, Philadelphia, Pa.

Every physician has had the frustrating, even exasperating, experience of trying to help a patient and finding it difficult to do so. While we may consider such a patient as "the difficult patient", it is evident that there are as well certain features of the physician with all his knowledge and training which may contribute to the problem. It is more correct, therefore, to speak of the difficult doctor-patient relationship rather than the difficult patient. It is our feeling, as a result of several years of close supervision of senior medical students in the Comprehensive Medicine Clinic at Temple University Hospital, that the basic problem in attempting to take a history and treat patients with whom such difficulties arise are basically ones of communication. Our approach to the problem is to use Balint's conception of the patient's complaints and history as being "offers", while the physician's side of the transaction is known as "responses". Under these two headings, we then attempt to describe the most common sources of difficulties, either arising in the patient's offers or in the doctor's responses.

As to the first category, the offers of the patients, we find the following types most frequently encountered in medical practice:

1. the multiple complainer.
2. the stolid or uninformative patient.
3. the verbose or tangential patient.
4. the blamer or scapegoater.
5. the masochistic patient; the patient who receives gratification through suffering.
6. this category is what is known as the red herring; the patient who offers a calling card or symptom which is supposedly acceptable to the physician instead of some more disturbing or difficult problem that the patient will only bring out if the physician is skillful or perceptive enough to detect it.
7. the hysterical or dissociated patient.
8. the psychotic or ex-mental hospital patient.
9. the depressed patient, especially when suicidal.
10. the hostile or arrogant patient who is critical of the physician.

With regards to the responses of the doctor, we list the following as being common sources of difficulty in communicating with patients:

1. the physician who believes that he is a stone god devoid of any emotion.
2. the apostolic function of the physician, as it is called by Balint, may frequently interfere with the physician's ability to hear what the patient is saying and to treat the patient to the best of his ability.
3. feelings of frustration or rejection in the doctor arising as a result of the stresses and strains of medical practice.
4. the tendency of the physician to over-identify with patients rather than to be able to use the optimal attitude of empathy.
5. the tendency of the physician to intellectualize and to professionalize his countenance and manner with the patient.
6. the tendency of the physician to respond to the manifest complaint in a hurried and superficial manner rather than detecting more meaningful and less obvious problems in the patient. In the same way, the treatment of a chance, objective finding rather than listening to and searching for the more meaningful reasons for the patient coming to see the doctor is another form of reponse making communication difficult.
8. response of the same sort is the tendency to reassure and advise the patient prematurely and hastily rather than hearing out and understanding.
9. the tendency of physicians to remain on the periphery of the intimate, personal details of the patient's life, particularly the sexual area, can be considered as a block in communication with the patient.

In our experience, we have found various modifications or parameters in interviewing technique which have served the purpose of overcoming the difficulties commonly encountered in everyday medical history taking. These are partly adaptations of psychiatric history taking and are frequently used to cut through or to search under the surface, particularly in patients who have emotional problems or psycho-physiological disorders. These are usually the most frustrating and difficult of all patients encountered in medical practice, even by experienced physicians. We will merely list these modifications in the history taking and they will be enlarged upon in the formal discussion.

1. non-verbal communication—observation of the patient's appearance, attitude and manner.
2. the detection of feeling tone or affect in the patient and enhancement of the physician's empathetic ability.
3. key-word and loaded phrases.
4. the patient's fantasy about the illness.
5. open-end questioning.
6. circumstances surrounding the onset of the symptoms.
7. fantasies and daydreams.
8. dreams.
9. earliest memories.
10. careful questioning oneself about the patient's questions to the physician.
11. careful observation and notation of the opening and closing remarks of the patients in the medical encounter.

Finally, we might note that any educative or maturing procedures which enable the physician to approach the problem of the patient's sexual life would have the effect of improving the physician's skill in dealing with such matters in medical history taking. This last is a tremendous undertaking greatly needed in medical schools today.

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Abstract 6

Depressive Reaction in Internal Medicine. Joseph W. Slap, M.D., and John H.

Nodine, M.D. Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

Depression is commonly seen in general medicine, either as a primary manifestation or as a consequence of physical illness. The physician may choose to do nothing about a depression brought on by a realistic blow of fate if the patient seems to be coping with it.

Often this is not the case. It is then necessary for the physican to intervene. He has a number of ways in which he may help his patient: psychotherapy, drugs and consultation with or referral to a psychiatrist. He may employ various combinations of these approaches.

Psychotherapy may uncover the underlying cause of the depression if this is not apparent. Often a patient who suppresses feelings of anger arising from some rejection or disappointment will develop depression without understanding its origin. If the patient can be made to understand and ventilate these feelings the depression may lift. In other cases, simply reassurance and optimism may be of great benefit.

The drugs available for the treatment of depression may be divided into mild and potent antidepressants. The former group consists largely of the sympathomimetics; the latter consists of the iminodibenzyl analogues and the monoamine oxidase inhibitors. The monoamine oxidase inhibitors tend to have serious toxicity problems and should be used with care.

Electroshock is a potent instrument in the treatment of depression, but is administered only by psychiatrists.

Referral to a psychiatrist should be considered where the patient is so depressed as to be inaccessible, where the methods of the internist have not been productive, where the patient might derive benefits from insight therapy beyond the lifting of the depression, and where there is danger of suicide.

Abstract 7

BEHAVIORAL REACTIONS TO SURGICAL PROCEDURES. Floyd S. Cornelison, Jr., M.D. Department of Psychiatry, Jefferson Medical College, Philadelphia, Pa.

In this paper the author discusses behavioral reactions to surgical procedures as an integral part of the illness complex which the patient may present. Of all the physicians who observe the responses of patients to operative surgery, the surgeon, not the psychiatrist, is the more experienced. It is only the unusual or abnormal response which brings the psychiatrist into the picture.

Four phases involved in the experience of surgery are discussed. The *anticipation phase* occurs when the patient has been told of the need for surgery and there is time for him to think about it before reaching the operating table. This encompasses the patient's feelings about himself and his body, his feelings towards his surgeon, his friends and his family. It also involves his feelings about pain, permanent damage and possible death.

Excessive anxiety and fear can be interpreted as a threat of castration or the loss of primary sexual apparatus. Operations early in life accentuate fear in the child of loss of body parts.

Psychological reactions to the surgeon are important, since the patient's attitude may depend a great deal upon his feeling about the person responsible for removing or modifying a body part. In many instances the physican takes the place of a parental figure although there may be no conscious awareness of this in the patient.

The *procedural phase*, for the most part, can only be judged by the surgeon and the anesthetist. Excessive movement of the patient during the operative procedure does not necessarily mean a behavioral response; it may be part of the anesthesia state.

During the *recovery phase* the patient thinks about the operation—whether it was successful or not, whether he will die, whether further surgical procedures are indicated. In other words, the patient is attempting to find out how intact he is. He is very concerned about his relationships with people, with time, space, mass and energy.

The *assimilation phase*, or final phase, is merely an extension of the recovery phase. Since life is not static, however, the final adjustment really rests upon the patient's life circumstances, his background, his personality and his capacity to respond.

In reviewing the literature regarding the many reactions to surgery, the author is impressed by the fact that the human reaction to threat of loss of body part or death has been emphasized, rather than the hope of recovery of important functions or even a new lease on life *because* of the surgery.

In other words, more often than we may realize, surgery can and should represent more security to some patients than a threat to their very existence. Perhaps this may account for the common observation that long-term serious mental illness is seldom precipitated by surgery. Even acute psychotic reactions to surgery are usually brief.

Abstract 8

Illness as a Way of Life. J. Elizabeth Jeffress, M.D. Department of Psychiatry, Woman's Medical College of Pennsylvania, Philadelphia, Pa.

The author describes a specific type of character disorder which has as its chief feature the patient's proneness to illness. The patient with this disorder is similar to patients with accident proneness, drug or surgical addictions. The link with the emotional life is usually completely outside the awareness of the patient, and, therefore, the illness is considered even more difficult to "cure" than patients with character disorders, serious depressions or even psychosis. By way of contrast, the latter group of patients often have some awareness of the part played by the emotional life in the production of their symptoms.

Clinical examples are cited to illustrate the use of illness as a means of communication and as a means of coping with anxiety and frustration. These patients often have little interest in their actual physical condition and particularly do not want to hear of any improvement in their condition.

The genesis of this personality pattern is seen to be in the early mother-child relationship where the child unconsciously complies with the mother's wish to keep the child sick and dependent. Since it involves the entire personality structure, this patient can be distinguished from other patients whose acute illness is triggered by a situation of emotional stress.

The consequences of a too early psychiatric referral are discussed. The author feels that the management of these patients must remain in the hands of the general practitioner or internist as the patient cannot stand to focus his problems in the emotional realm without a great deal of support from the physician.

Abstract 9

Hyperglyceridemia and Atherosclerosis. Peter T. Kuo, M.D.‡ Robinette Foundation for Cardiovascular Research, Medical Clinics, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Several investigators have reported on the close association between hyperglyceridemia (hyperlipemia) and clinical atherosclerosis. Schrade, Albrink, Carlson, Gofman and others have made comparative studies on the serum triglyceride levels of healthy and atherosclerotic subjects in different age groups.

In reviewing our own patients with hyperlipidemia and clinical atherosclerosis, we found that they may be classified into two main groups, according to their plasma lipid patterns: (1) A pattern of "pure" hypercholesteremia with no elevation in the serum triglyceride level. This pattern is obtained in patients with essential familial hypercholestere-

‡ This work was done during Dr. Kuo's tenure as Research Career Development Awardee (Grant 5-K3-AM-17,012), National Institutes of Health, U. S. Public Health Service, Bethesda, Md. Support was also received in grants from the American Heart Association; from the Pennsylvania Heart Association; from Grant HE-08805, National Heart Institute, and from the Clinical Research Center Grant 3-MO-1-FR-40, Division of Research Facilities and Resources, National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

mia. It is interesting to note that in the older and overweight members of the family, this pattern may be complicated by the development of mild to moderate hyperglyceridemia. (2) In cases of hyperglyceridemia, which is the main subject of this discussion, serum cholesterol, phospholipid and triglyceride concentrations are all elevated. But the serum triglyceride fraction is chiefly involved. Although patients with marked hyperglyceridemia with xanthomatoses and lipemic retinale are relatively uncommon clinically, mild to moderate degrees of hyperglyceridemia are the most frequent form of hyperlipidemia encountered in atherosclerotic patients.

The mechanism of production of hyperglyceridemia has not yet been satisfactorily defined. Hence, its classification has been rather confusing. Tentatively, we believe, it may be classified into the: fat-induced, carbohydrate-induced, and the "mixed" (fat and carbohydrate induced) types.

We and a few other investigators have presented evidence to show that the so-called abnormal fat tolerance curve frequently demonstrated in patients with coronary artery disease, it is not related to a "delay in clearing of the lipemia" in the great majority of these patients. It is rather closely correlated to the degree of hyperglyceridemia and to the enlarged body triglyceride pool of the patient. The abnormal fat tolerance curve would invariably return to normal following the reduction of the elevated blood lipid levels to normal.

A relative decrease or deficiency in the heparin-stimulated lipo-protein lipase has been implicated in the production of hyperglyceridemia in atherosclerotic patients. Recent studies made by Fredrickson and his associates and by ourselves, indicate that the enzyme is indeed low in patients with "fat-induced" hyperglyceridemia. However, no premature development of atherosclerosis has been observed thus far in patients with this type of lipemia. In patients with the carbohydrate and the "mixed" types of hyperlipemia, which are known to have a close association with atherosclerosis, their plasma enzyme levels are either normal or elevated. Therefore, it is unlikely that a deficiency in lipemia-clearing enzyme is the basis for the production of the commonly encountered type of hyperglyceridemia.

Recent studies from our laboratory point to an exaggerated endogenous lipogenesis as the chief mechanism in the production of hyperglyceridemia in patients with coronary artery disease. While severe degrees of hyperglyceridemia can readily be induced in these patients by high carbohydrate feeding, we now found that sugars, especially sucrose, are much more potent hyperglyceridemic agents than starches. In addition, in practice, a high sugar intake makes it difficult to control the total carbohydrate calories in the diet of these patients. The data suggests that high sugar, high carbohydrate intake actually initiates hyperglyceridemia and secondary hypercholesteremia in certain susceptible individuals. The accumulation of excessively synthesized lipids gradually expands the body triglyceride pool which then serves to trap food fats to further its expansion and finally results in clinical hyperglyceridemia.

Varying degrees of sugar restriction have been used to reduce the carbohydrate intake of our hyperglyceridemic coronary patients. These programs, despite the relatively high dietary saturated fat contents, have been effective in controlling the hyperglyceridemia as well as hypercholesteremia of our patients for prolonged periods of time.

Abstract 10

LONG-TERM EFFECT OF HEPARIN ON FAT TOLERANCE TESTS Asher Woldow, M.D. Department of Cardiology, Albert Einstein Medical Center, Northern Division, Philadelphia, Pa.

It has been noted in the past that following a fat load meal, patients with coronary artery disease have a more severe and prolonged lipemia than do normal individuals. Generally, this difference is also noted in the fasting levels. Heparin administered in small doses

will clear this turbid lipemic serum in most patients.

We have previously reported that heparin given in an attempt to prevent the expected post-prandial hyperlipemia, was, instead, followed by rebound lipemia, which in most cases was more severe than when no heparin was used. These results were found to be independent of whether the dosage was given intravenously, intramuscularly or subcutaneously. These were also independent of dosage.

Many of the above patients were then given multiple doses of heparin at 4 hour intervals, for from 20 to 22 doses, and the fat tolerance tests repeated. Rebound did not occur and prolonged serum clearing was maintained.

With this background, we have now treated 16 patients with coronary artery disease—as out-patients. They have taken injections of 50 to 100 mg. of heparin at intervals of 1 to 3 times daily. They have not been asked to alter their dietary intake. Most cases have been kept on 50 mg. doses taken at 12 hour intervals.

Some of the reactions noted were the annoyance by frequent injections, itching at site of the injection, flushing, generalized hives, and subcutaneous hemorrhages. The patients have been on the medication for from 1 to 18 months. Six of our cases are not reported here because of only one follow-up study having been completed to date. The 10 remaining cases included 5 with post-prandial hyperlipemia and 5 showing either no or slight hyperlipemia. The studies included turbidity of serum, triglyceride levels, cholesterol and beta-lipoprotein levels. The significant results noted were in the triglyceride and turbidometric readings.

In the hyperlipemic group we see that there are from good to excellent results in response to a fat load meal. The results in the fasting levels were not as dramatic, but the triglyceride results appeared better than did the turbidity levels. This carried through at the three-hour postprandial level. At 5 hours the most dramatic results were noted, here in both turbidity and triglycerides.

In the less lipemic group, results apparently were unsatisfactory. It is noted that in no cases—whether fasting, 3 or 5 hour post-prandial—was there any significant persistent clearing of the serum. At times, even rebound hyperlipemia occurred. We suggest that this may be, at least in part, an absorption effect on the gastro-intestinal tract.

In conclusion, we believe that if more studies can confirm the above findings, then only specifically hyperlipemic patients may be candidates for long-term heparin therapy. We would then suggest finding the optimal dosage and frequency for heparin usage. An oral heparinoid substance would be essential and, finally, long-term effect on clinical coronary artery disease could be determined.

Abstract 11

ISOLATION AND QUANTITATION OF PLASMA SEX HORMONES IN PATIENTS WITH CORONARY ARTERY DISEASE. Henry S. Kroman, PH.D., Sheldon R. Bender, M.D., and Alfred N. Brest, M.D. Section of Vascular Diseases and Renology, Hahnemann Medical College and Hospital, Philadelphia, Pa.

Female sex hormones have been observed to alter abnormal serum lipid values in the direction of normal. This and the observed rarity of myocardial infarction in pre-menopausal women suggests their implication in the genesis of coronary artery disease. The purpose of this study is to determine the qualitative and/or quantitative differences that may exist in the female sex hormones when comparing asymptomatic normals to a comparable group of patients with documented coronary artery disease.

The hormones (estrone, 17β-estradiol and estriol) were chemically extracted and subsequently separated by gas chromatography as described by Kroman *et al.* (Clin. Chim. Acta. **9**:73, 1964). Total cholesterol, triglyceride and lipoprotein per cent composition were determined by conventional techniques.

Results indicate that of 100 normals (males and females, age range 20–58 years), 96 per cent (96 cases) showed a higher concentration of 17B-estradiol than estrone. In 100 male

and female patients with coronary artery disease (age range, 30–70 years), 92 per cent (92 cases) exhibited a higher concentration of estrone than 17B-estradiol. No significant differences were noted in the concentration of estriol.

These results suggest a metabolic abnormality in the formation of the female sex hormones (estrogens) under conditions prevalent in coronary artery disease.

Abstract 12

CURRENT CONCEPTS OF THE TREATMENT OF HYPERLIPIDEMIA. William L. Holmes, PH.D. Smith Kline and French Laboratories, Philadelphia, Pa.

A considerable body of circumstantial evidence has implicated elevated blood lipids in the pathogenesis of atherosclerosis. As a consequence, a tremendous amount of research directed toward the chemotherapy of this disease has centered around attempts to control the concentration of lipids in blood and tissues.

This discussion will be concerned with the treatment of two types of hyperlipidemia, namely, hypertriglyceridemia and hypercholesterolemia. It is now generally accepted that there are two distinct types of hypertriglyceridemia, either fat- or carbohydrate-induced; many patients probably present a mixture of the two. The first of these, involving an elevation of the concentration of circulating chylomicrons, can be controlled by regulating both the caloric and fat intake. There are presently no drugs available for treating the fat-induced hypertriglyceridemia; however, consideration of present knowledge concerning digestion and absorption of dietary fats suggest that this may be a fruitful field for future research. The carbohydrate-induced variety of hypertriglyceridemia is characterized by an accumulation of triglyceride in the pre-β-lipoprotein of plasma. The triglyceride involved is synthesized in the liver from carbohydrate and free fatty acid. The possible mechanism of such drugs as heparin, nicotinic acid and p-chlorophenoxyisobutyric acid in controlling this type of hyperlipemia will be discussed.

Finally, some aspects of the problem of hypercholesterolemia will be reviewed. Consideration will be given to a number of theoretically feasible approaches for controlling body pools of this sterol. These involve inhibition of cholesterol biosynthesis, increasing its rate of catabolism and excretion, and interference with its absorption and reabsorption from the gastrointestinal tract. During this discussion, brief mention will be made of several drugs now in use or under investigation in each of these areas.

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The Human Heart: Some Aspects of its Excitation[1]

By PROFESSOR DIRK DURRER[2]

MY FIRST steps in experimental electrocardiography, a slippery and dangerous field as I now know, were initiated by the contact with the work of the Wilson School in the immediate post-war period. Before Dr. Frank N. Wilson, the reading of electrocardiograms was like determining the origin of a stamp: one looked up in a book the illustrations resembling as closely as possible the record considered. One then copied the legend of the illustration and the job was finished. Wilson and his school changed this. They introduced logic into interpretation of EKG's. Application of a certain set of rules, obtained by a careful analysis of electrocardiograms and by animal experiments, made it possible to arrive at a conclusion, which was often corroborated at the autopsy table. A hint in one of the articles of Wilson put me on the tract I pursued for many years: he tried to explore the inside of a dog's heart. When I got the opportunity to do some research, there were many reasons to try to explore the hidden and mysterious interior. In these post-war years electrocardiography resembled in many respects the situation of the geographic map of Africa at the middle of the 19th century: only the peripherally lying portions had been explored, the interior was almost a complete blank. Even in the canine heart, so much more readily available for experimental analysis than the human heart, very little was known about the electric activity of the A. V. node, the His bundle, and the subendocardial Purkinje system. The pathway of excitation in the ventricular septum and walls was known only in general outline and in the case of the ventricular septum the accepted concept was wrong. A very good analysis of septal excitation by a German veterinarian, Schneider, published in 1915, was forgotten, as are so many results of great importance in electrocardiography, swept away by the tidal wave of EKG-literature. In the past two decades and due to the work of many investigators this situation—so far as the canine heart is concerned—has changed. However, our knowledge of the time-course of excitation of the human heart is still in a rudimentary stage. But is it necessary for clinical electrocardiography to map the time course of excitation in the human heart in all its details, to describe the rapidly and continuously changing boundaries between resting and active muscle occurring during depolarization? Some clinicians are of the opinion that the simple concepts already established are quite adequate to interpretation of clinical

[1] Mary Scott Newbold Lecture LXXXIX, The College of Physicians of Philadelphia, 7 April 1965.

[2] University Department of Cardiology, Wilhelmina Gasthuis, Amsterdam, The Netherlands.

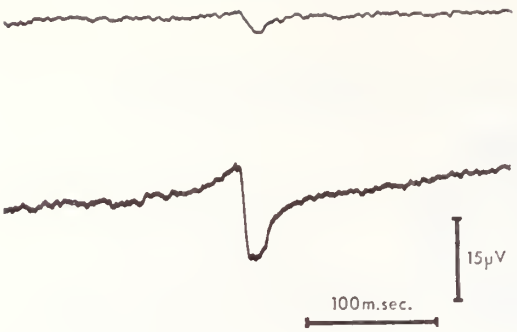

FIG. 1. Unipolar complex of rS form, recorded in a culture of heart muscle cells. The intrinsic deflection is clearly visible.

records. I wholeheartedly disagree with this opinion, and want to give four reasons.

1) It is forgotten that this concept is the result of animal experiments, and that similarity in form of complexes does not necessarily indicate a same origin of the deflections (Fig. 1).
2) Great differences exist in the excitation pattern in different species. Even in the same species the time course of excitation changes with increasing age. Conduction velocity of the excitatory wave in a normal young dog is about 50 cm/sec. When 10 years old and apparently normal, it slows down to 30 cm/sec. Interestingly enough this decrease is not the same for all parts of the ventricles.
3) Existing concepts rest on unproved premises. It is commonly assumed that the nadir of the Q indicates subendocardial excitation, and that therefore the time interval between the nadir of the Q wave and the intrinsic deflection defines the time consumed by the excitatory wave in travel only from endocardium to epicardium. Experimental evidence supporting this view was never provided, but the idea has been generally accepted. It is wrong, however, because at the moment the Q nadir is written, a relatively large part of the inner layers may be activated already.
4) With our present knowledge of human excitation it is not possible to explain certain electrocardiographic features, as for example the W.P.W. syndrome, the A.S.D. I vector with its remarkable diagnostic specificity, left axis deviation, many details of the changes in the QRS complex in chronic infarction, etc.

That we are relatively content with the present status of electrocardiography, is an expression also of a very bad habit of our days: the use of the direct writing apparatus without high-frequency response. In this way a lot of information is lost and the recorded residue is but a flimsy remnant of what the heart is trying to tell, and easily explained by the commonly used but highly schematic excitation pattern. The only way to find the solution of these problems is the exploration of excitation in the human heart itself; this was the way used nearly 30 years ago by Barker *et al.*, to solve the bundle branch block controversy.

But this motivation is a poor one indeed when compared with that given by Helmholtz in 1853. He stated that measurements of potentials on the surface of the tissue, or formulated more generally, determination of the external field of current, is insufficient to ascertain the location of the internal electromotive forces, since an infinite variety of forces could produce one and the same field of external current. Therefore it is necessary to determine directly the structure of the unique generator, i.e. the time course and instantaneous distribution of the excitatory wave.

Many sources of information for the study of human excitation are available:

A. Intrathoracic exploration
   1. intrathoracic electrodes, introduced by puncture or via bronchoscope
   2. catheterization of pulmonary artery branches or pulmonary veins
B. Epicardial exploration
   1. catheterization of cardiac veins
   2. epicardial exploration during surgery
C. Intramural exploration during surgery
D. Intracavitary exploration during heart catheterization
E. "Autopsie physiologique".

Many ways lead to Rome, and many to the heart, but only the combination of epicardial and intramural exploration in which precise

localization of the exploring electrode is possible, gives satisfactory results. It is the most satisfactory and rewarding way to explore human excitation, but only possible during cardiac surgery. Many drawbacks are evident. No one wants to delay unnecessarily a difficult operation. Our surgeon allowed us 10 minutes and no millisecond more to explore the heart and introduce one intramural electrode.

Epicardial Excitation

Many of the published results of epicardial exploration studies must be accepted with due regards of certain shortcomings.

1) In many instances a low frequency, direct writing apparatus is used: it is as easy as it is wrong. A high-frequency apparatus is essential.
2) Application of the exploring electrode at the epicardial surface was not done under visual control; the pericardium has to be opened.
3) The reference lead used is often a peripheral one. There is, however, a varying time difference between the beginning of this peripheral complex and the beginning of depolarization of the ventricles, which may amount to 20 msec, sometimes probably even more. Respiration may change this time difference. The only acceptable reference lead is a unipolar one from the left or right ventricular cavity. It can be shown, that the beginning of QRS in such cavity leads coincides within narrow limits with the beginning of ventricular depolarization.

Influence of Opening Thorax on Form Epicardial Complexes

I want to point out that the intrathoracic electric field of the heart and its epicardial potential distribution is changed by the opening of the thorax. There is a decrease in voltage of the positive deflections, the negative ones becoming deeper. In the human heart, comparing precordial and epicardial complexes, we always found at the epicardial surface complexes like those found over the intact precordium. This indicates that the influence of opening of the thorax is not so great that major differences in form occur under these circumstances. In the dog's heart we proved, moreover, that the time of occurrence of the intrinsic deflection was not altered by opening the thorax.

Form of the Epicardial Complexes

I will not give a systematic description of the form of the right and left ventricular complexes recorded from the human heart, but for those familiar with findings in canine hearts, the similarity of these forms from corresponding sites is striking. In the epicardial complexes of the human heart the intrinsic deflection is always clearly visible. The portion of this fast deflection, signalling the arrival of the excitatory wave, has a duration of about 1 msec, and the drop in potential may be 20–25 mV. The use of the left ventricular cavity complex as a reference discloses that the beginning of the Q wave in epicardial leads does not necessarily coincide with the beginning of the left ventricular cavity complex: an iso-electric part of the R wave with a duration of 10 msec sometimes precedes the Q. The nadir of the Q wave does not signal the beginning of subendocardial excitation.

Excitation of the epicardial surface is essentially a double envelopment of both right and left ventricular surfaces starting in the area trabecularis and progressing with a speed of about 2 meter per second towards the posterobasal region of the heart where they collide. Epicardial excitation can give information only about excitation of the subepicardial muscle layer and not about total excitation, a deduction which rests on Helmholtz' theorema.

Intramural Excitation

For the study of subendocardial, intramural and septal excitation we have developed a method which can also be applied in the human heart at thoracotomy or on hearts revived post mortem. This intramural technique may have several shortcomings. The introduction causes:

1) destruction of tissue.
2) focal block with delay in excitation, due to pressure of the electrode on the muscle surrounding the puncture canal.

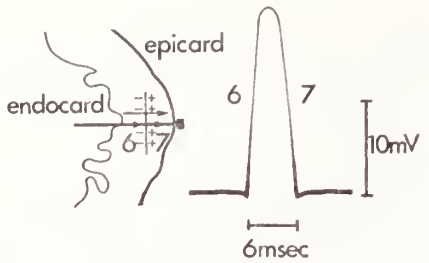

Fig. 2. Schematic representation of two intramural terminals (6 and 7) with the excitatory wave between them, travelling towards the epicardium. The complex registered between 6 and 7 is shown. The fast deflection in the upstroke signals the arrival at terminal 6, the one in the downstroke at terminal 7.

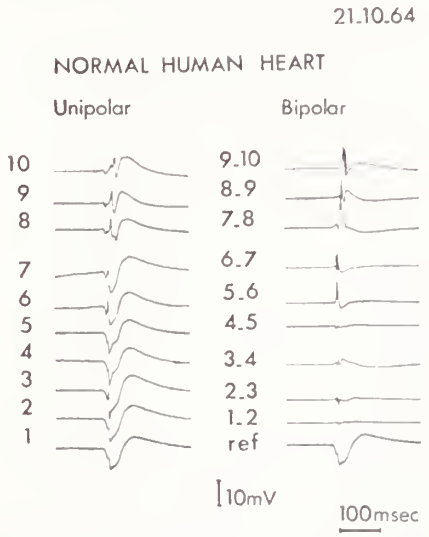

Fig. 3. Unipolar complexes from the left ventricular wall (left). From terminal 5 there is an outward spreading excitatory wave, as can be seen from the complexes recorded between consecutive terminals (right). The small complexes in the inner layers, are probably caused by the trabeculated structure of these layers.

Movement artefacts may cause a continuously irregular baseline and changing form of the intramural complexes. I think that with the intramural electrode we devised, these artefacts are nearly completely prevented. In the operating room these shortcomings may be increased, because little time is available, and this precious time cannot be lost by waiting. The injury and focal block are therefore taken for granted and the records interpreted with due regard to their shortcomings.

Technique of Intramural Exploration

Terminal 1 is situated in the ventricular cavity, while 10 is lying in the subepicardial muscle layer. In complexes, recorded between consecutive terminals of the intramural electrode, positivity indicates the existence of outward spread in the muscle layer between the terminals (Fig. 2). Time relations of excitation are measured by the time of occurrence of the fast deflections in unipolar and bipolar complexes.

Results of Intramural Exploration

The intramural complexes (Fig. 3) show a gradually increasing R wave in the middle and outer layers with progressive delay in time of occurrence of the intrinsic deflection towards the epicardium. In the inner layers this uniform pattern may be absent. The bipolar complexes of a normal left ventricular wall from a patient

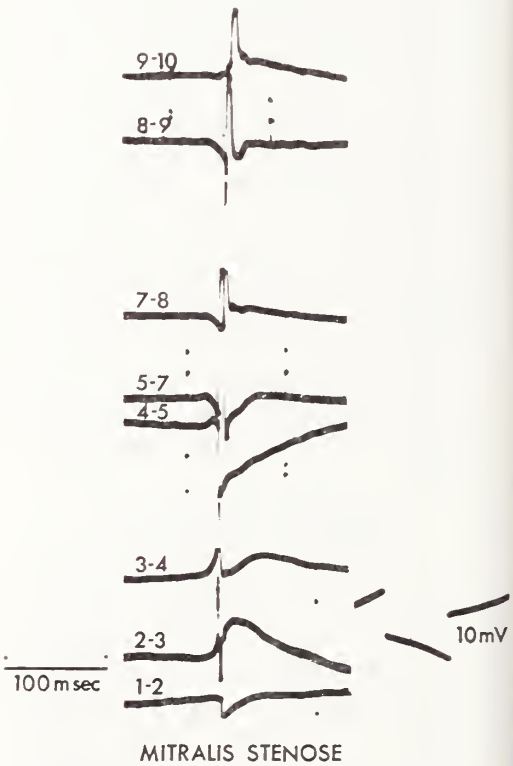

Fig. 4. Intramural complexes between consecutive intramural terminals from the left ventricular wall of a patient with mitral stenosis. Terminal 6 was defect. There is an outward spreading excitatory wave from terminal 5 towards the epicardium (10).

with mitral stenosis are given in Fig. 4. There is a nearly constant outward movement of the excitatory wave across the thickness of the ventricular wall. The time relations indicate that conduction velocity will be no more than 30 cm/sec.

Physiologic Parameters Influencing QRS Form and Duration

Before trying to assemble the fragmentary data about excitation of the human heart into a hypothetical schema of the pathway of excitation of the normal human heart, it is necessary to give some relevant data about the form of the 1) *membrane action potential*, 2) *intramural conduction velocity*, and 3) *time of occurrence of subendocardial activation*.

Membrane Action Potential

A very important parameter is the form of the human membrane action potential. In an isolated human heart we could record the membrane action potential of one single, normal cell, and study the changes in the form caused by changes in rate of heart beat. Depolarization does not last more than 1 msec at all rates. The upstroke coincided with the rapid part of the intrinsic deflection of the unipolar complex registered before entering the cell. A very interesting finding was that phase 3 of the membrane action potential has a constant form during widely varying heart rates (29–86/min.). Therefore, in this instance the changes in the duration of the membrane action potential are caused by changes in duration of phase 2, phase 3 remaining constant. The duration of this phase, responsible for the T wave, is about 200 msec at all frequencies.

Conduction Velocity

Essential for the analysis of excitation is the determination of conduction velocity. Accurate results can only be obtained if the excitatory wave progressing along the muscle fibers bordering the puncture canal is propagated in a direction parallel with the axis of the intramural electrode. This occurs if two adjacent terminals of the intramural electrode, situated in endocardial or epicardial muscle layers, are used as stimulating electrodes. It is impossible to perform these measurements during surgery, but we had the opportunity to do it in the isolated human heart. Here we found the speed to be about 30 cm/sec. Therefore the transition zone present between resting tissue and tissue in completely depolarized state is not greater than 3/10 mm.

Subendocardial Activation

The last important pillar on which our schema of total excitation stands, is the time of occurrence of subendocardial excitation. Up to now we do not have a sufficient number of insertions in a normal heart to give an accurate analysis of time relations of subendocardial excitation of the left and right ventricular walls and ventricular septum. We can, however, estimate roughly subendocardial excitation time by using epicardial excitation time, conduction velocity and diastolic thickness of the ventricular wall.

It takes about 10 msec after depolarization of the subendocardial Purkinje system before a 5 mV potential is generated in a bipolar complex in the subendocardial layer in contact with these Purkinje fibers.

Diastolic Thickness Human Heart

The only satisfactory report I found about measurements of diastolic thickness of the ventricular wall of the human heart, was published by Koch in 1925. He removed the hearts from killed soldiers, 15 minutes after death, and prevented the occurrence of changes in heart-form by the rigor mortis. In these hearts the left and right ventricular cavities are much larger than in dogs' hearts with the same diastolic thickness of the wall.

Total Excitation

Fig. 5 depicts this very first approach to normal human excitation. It resembles the total excitation pattern of the dog's heart. Epicardial excitation times at corresponding points and total duration of excitation are increased. The overall movement of excitation present in the dog's

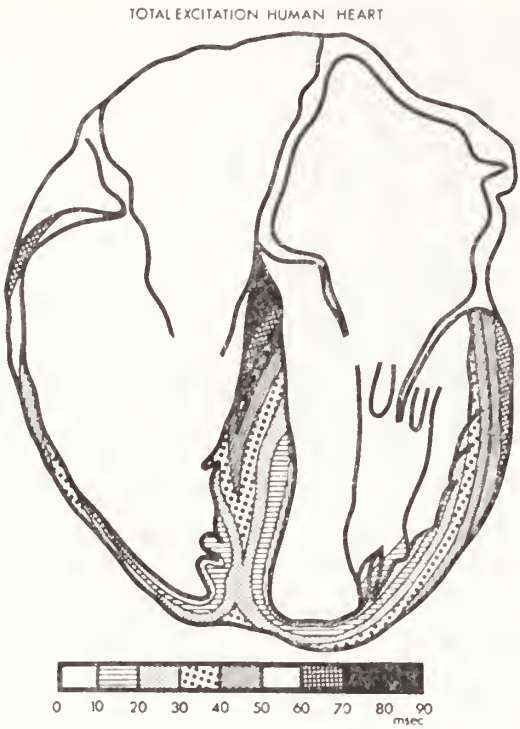

FIG. 5. Schematic representation of total excitation of the normal human heart "with some pretense to accuracy" (Sir Thomas Lewis).

heart, *i.e.*: the double development of both ventricles and of the septum is here clearly visible too. It was assumed, that those parts of both surfaces of the septum at which excitation first occurs, are activated at the same time or with a very small time difference. An exploration of the exposed ventricular septum of the dog's heart under visual control revealed that Purkinje spikes in these areas occurred synchronously. I assumed this is also the case in the human heart. In the dog's heart relatively great differences in size and location of area supplied by the left and right bundle were found, and there is no reason to expect that this variability is less in the human heart. This schematic representation of total excitation explains the form of the complexes recorded at different sites of the heart. Initial positivity of the right ventricular cavity can be explained by the larger size of the rightward progressing boundary initiated by the left bundle, than of the leftward moving one produced by the right bundle.

After collision of these two excitatory waves, the movement progresses in a predominant upward and basal direction. This movement is caused by the absence or scarcity of Purkinje fibers in the basal part of the ventricular wall, mainly in the posterior area. The crista supraventricularis and right ventricular outflow tract belong to the latest activated parts of the ventricles. That is the reason that the last part of the QRS complex is written after epicardial breakthrough at the posterobasal area.

Right Ventricle

Probably no intramural Purkinje distribution of significance is present. The larger part of the right ventricular wall is activated mainly in a tangential direction, a phenomenon also caused by the "absence" of Purkinje fibers. Epicardial activation times of the basal areas are therefore late.

Left Ventricle

In those parts of the left ventricular wall of the normal heart we could explore, no appreciable Purkinje penetration is present; there appears to be a continuous outward movement across the ventricular wall as illustrated by the form and time relations of the unipolar and bipolar complexes. Inward movement, as frequently found in the apical half of the ventricular wall of the dog, which we have attributed to intramural Purkinje penetration, has not been found up to now. If inward movement of excitation is present, it is confined to the innermost layer and can be explained by the trabeculated structure of that region. The electric effects of excitation of the inner layers on the form of the epicardial complexes is small compared with those of the outer layers of similar thickness. The greater distance towards the exploring electrode is an important factor. Cancellation due to the occurrence of small excitatory processes progressing in many directions in the trabeculated structures, is another one. Because intramural Purkinje

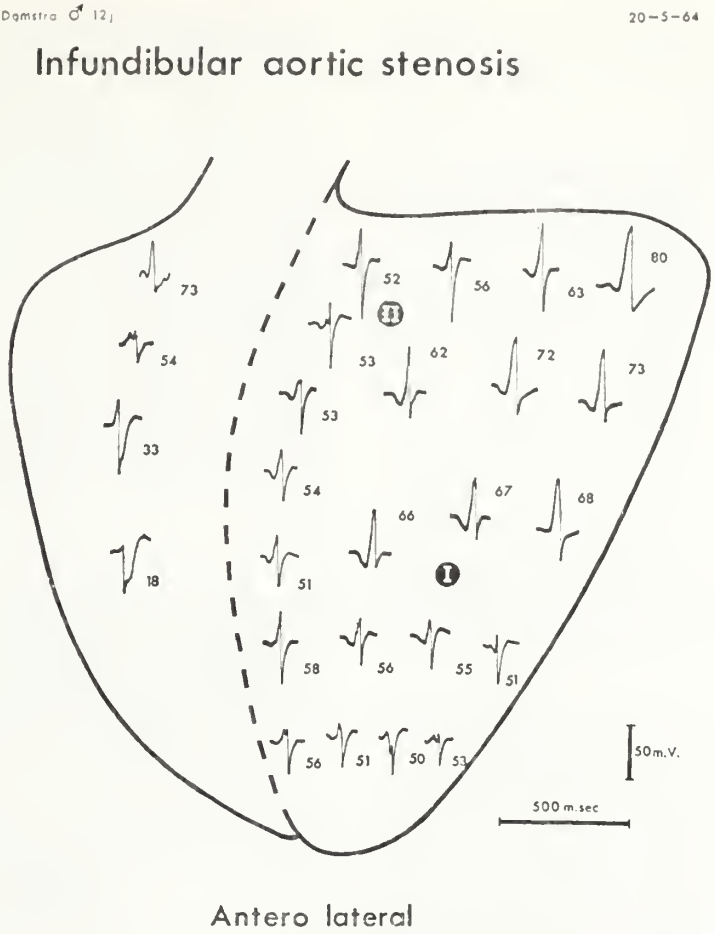

FIGURE 6. Unipolar epicardial complexes from a patient with infundibular aortic stenosis, recorded during surgery. At point I an intramural electrode was introduced into the ventricular wall.

penetration probably is almost completely absent in the normal human heart, it does not increase cancellation as it does in the dog's heart.

RIGHT VENTRICULAR HYPERTROPHY

We had the opportunity to explore a few cases of right ventricular hypertrophy without conduction delay in the right bundle branch as proved by the existence of early Purkinje spikes in the subendocardial layers. A delay in epicardial excitation time was found, but this delay was not uniform for all points explored. The overall movement of epicardial excitation is unchanged, compared with normal excitation.

The outer layers of the hypertrophic right ventricle cause the same voltage of bipolar complexes as the normal left ventricle (about 20 mV). Conduction velocity of the outward moving excitation wave apparently does not differ much from 30 cm/sec. For every millimeter of increase of the ventricular wall a delay of 3 msec should occur. The non-uniformity of epicardial excitation delay is probably caused, at least partly, by differences in increase of thickness. The regions with the largest radius of curvature, *i.e.*, near the base of the right ventricle, become thicker than those near the apex of the right ventricle with its smaller curvature.

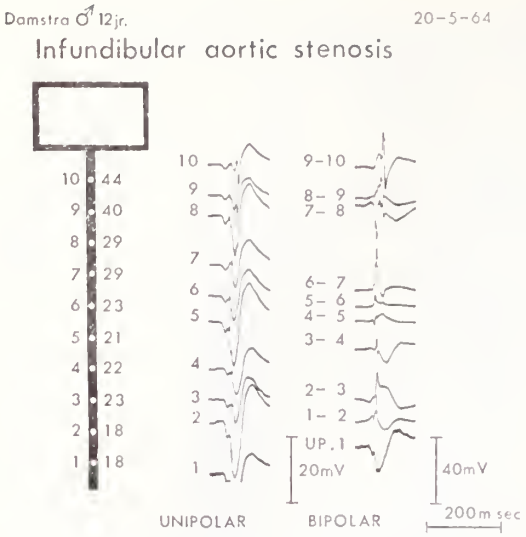

FIG. 7. The intramural bipolar complexes from the same patient with hypertrophic infundibular aortic stenosis are grossly abnormal. The voltage of some of the bipolar complexes (9-10) has increased.

I want to point out that in right ventricular hypertrophy nothing is known about:

1) distribution of the area supplied by the right bundle branch;
2) the role of hypertrophy of the right part of the ventricular septum;
3) the influence of conduction delay, etc.

A careful analysis of the anatomic structure of the right ventricular wall and a quantitative analysis of the changes in anatomy is of great importance for the understanding of the electrocardiographic changes in right ventricular hypertrophy.

The precordial complexes in V3R and V1 in many cases of right ventricular hypertrophy resemble those recorded near the right atrioventricular sulcus at the right lateral border, whereas those at V4/V6 are similar in form to those from the area trabecularis. Here is an instance in which potentials from the right ventricular surface not only influence the right precordium, but also the left precordium.

LEFT VENTRICULAR HYPERTROPHY

Only in one instance of infundibular aortic stenosis with huge left ventricular hypertrophy epicardial exploration was possible (Fig. 6). At one point it was possible to introduce an intramural electrode into the ventricular wall (Fig. 7). Apart from the grossly abnormal bipolar complexes, one interesting feature was the increase in voltage of these complexes, particularly 9-10 situated in the outer layer. Here is a first indication that the increase in voltage so frequently found in the precordial complexes in ventricular hypertrophy may be due partly to an increase of the strength of the equivalent dipole generated by excitation of the muscle layers. Decrease in strength of the equivalent dipole layer was found in constrictive pericarditis and in coronary heart disease with diffuse fibrosis.

ASD I

Up to now the genesis of the typical vector loop with its superior orientation and anticlockwise rotation has defied all attempts for explanation. In four instances epicardial excitation of the right and left ventricular surface was carefully explored.

It became apparent that in both types of defects the excitation pattern of the right ven-

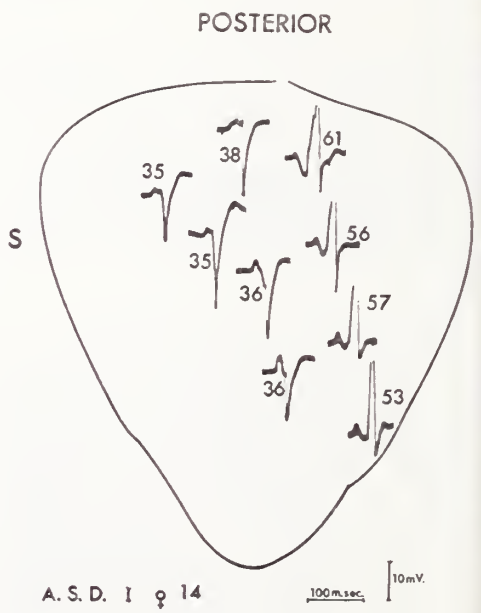

FIG. 8. Epicardial complexes from the posterior surface of the heart in patient with ASD I.

tricle was similar. At the posterior surface of the left ventricle near the ventricular septum and the A.V. sulcus we found in primum defects an area activated at least 30 msec earlier than usual (Fig. 8). In one case an intramural electrode could be introduced into that region, proving that the inner layers were activated in the very beginning of ventricular depolarization. The explanation of this finding is given by the anatomy of the specific conduction system. In ASD I the posterior fasciculus is short and supplies this region immediately after its origin from the common bundle. I want to point out the existence of great differences in epicardial excitation time in regions lying close together, but on different sides of the ventricular septum. This peculiar fact is not caused by a barrier in the ventricular septum, which we never found, but because of the absence of Purkinje fibers on the right side in that region. Moreover in the dog heart conduction velocity in a direction perpendicular to the fibre length is 50% less than in a direction parallel with it.

Chronic Myocardial Infarction

In view of the great diagnostic importance of the EKG it is remarkable indeed that so few papers are published about the basic problems of excitation in this condition. I want to mention some of these problems.

1. How does the excitatory wave reach the epicardial surface of the scar?
2. Do changes in function of the subendocardial Purkinje system play a role in the genesis of abnormal Q wave, as recently postulated?
3. Is it possible to predict from epicardial QRS changes the size and degree of intramural extensions?
4. What is the minimum size of the scar in the left ventricular wall detectable in epicardial leads and in precordial leads?
5. How does this minimum size depend upon the location of the scar?

Our methods for epicardial and intramural exploration made it possible to examine some of these problems in the dog's heart and recently in the revived human heart.

Epicardial exploration in the dog's heart with scars revealed that in many instances the area overlying the scar is activated late in the cardiac cycle, even after the end of the QRS complex. This delay is not caused by late excitation of the Purkinje fibres at the endocardial side of the scar. Excitation of the Purkinje fibres occurred at normal time. The main reason for the delay in epicardial excitation is the reduced conduction velocity of intra-infarction excitatory waves, propagated along surviving strands of muscle fibres. These excitatory waves may follow circuitous routes. In many instances it could be proved that during a 20–40 msec time interval excitatory waves were present at different depths of the scar. Even near the endocardial surface excitation may occur after the end of the QRS complex. Conduction velocity of the apparently normal muscle bordering the scar may be reduced too, proving the existence of peri-infarction block. Because of reduced conduction velocity of the excitatory wave a small zone of muscle at the epicardial side of a nearly transmural scar deprived of living muscle and activated in a tangential direction, may generate a high R wave. No cancellation effects of opposing excitatory waves are present at that time, because the remainder of the ventricles is depolarized. Therefore the relation of the depth of the Q to the height of the R wave does not indicate the degree of intramural extension of the infarction.

Detection and Minimum Size of Scars in Epicardial Leads

It is possible to delineate rather accurately the border of the scar, even in a subendocardial infarction confined to the inner layers. In our experiments on the dog's heart we never met an instance in which an infarction of the inner layers could not be detected in the epicardial complexes. Even a scar of a diameter of 1 centimeter and an intramural extension of a few millimeters was easily detectable. We concluded therefore that a silent zone, in which abnormalities do not give rise to changes in the epicardial complexes, is absent in the dog's

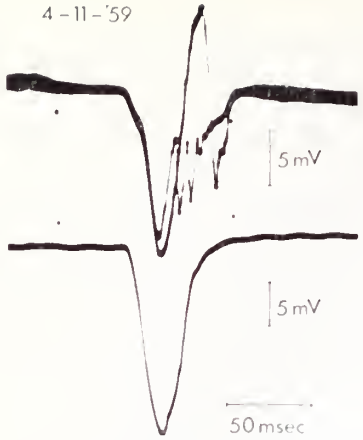

Fig. 9. Two superimposed unipolar epicardial complexes recorded from closely adjacent regions of a nearly transmural scar. The reference is the unipolar complex from the left ventricular cavity.

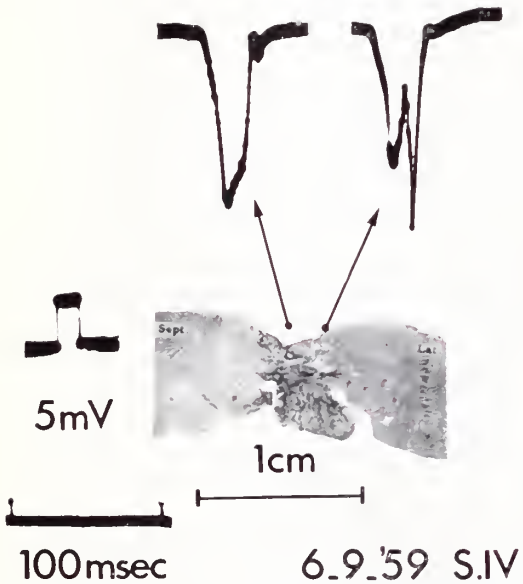

Fig. 10. Unipolar epicardial complexes from a transmural scar. The QS complex shows many small notches in the beginning of the descending limb and in the upstroke of the QS complex.

heart. Because excitation of the human heart does not differ in any essential way from the dog's heart, I think that this silent zone is absent in the human heart as well. These results

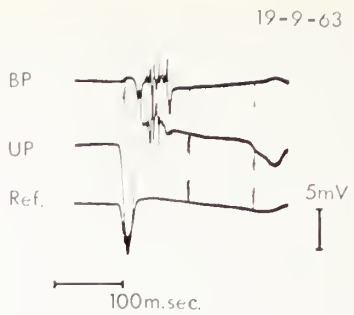

Fig. 11. Unipolar epicardial complex (u.p.) recorded from one of two closely adjacent electrodes (0.1 mm distance), located on the central area of a nearly transmural infarction, and the complex recorded between these two electrodes (b.p.). This epicardial region is activated late in the cardiac cycle. For at least 30 msec. excitatory waves are present in this small area.

prove that under our experimental conditions there is a definable local effect of depolarization of the inner layers in epicardial leads. The proximity effect of epicardial excitation is surprisingly great, however, as can be seen from the major differences in form of complexes in closely adjacent regions (Fig. 9).

Notching Epicardial and Intramural Complexes

The epicardial and intramural complexes may be highly notched. This notching may occur at every part of the QRS complex, but is often absent or of moderate degree in the abnormal Q wave of a scar of the endocardial half of the wall. It is probably caused by strands of muscle fibres in the scar. We have encountered it in a few instances in the QS complex of a transmural scar which includes large strands of intra-infarction fibres (Fig. 10). Notching of the R wave may be excessive, particularly if the muscle layer includes strands of fibrous tissue.

Desynchronized and Prolonged Excitation in Small Areas

Excitation may linger in a very small area for 40–50 msec, in all layers of the scar, even at the endocardial surface. The very small deflections in complexes from closely adjacent elec-

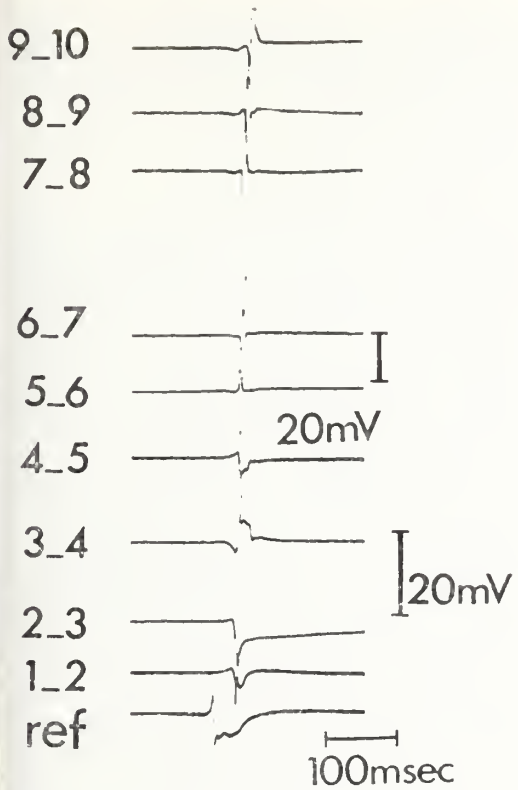

FIG. 12. Isolated human heart with multiple infarctions and diffuse fibrosis. Intramural electrode introduced into a normal, hypertrophic part. Only in the outer layers outward spread is present. Between 5–6 and 7–8 reversals are present, pointing to the existence of inward spread. They may be caused by intramural Purkinje penetration in this instance, but excitation of the ventricles was abnormal because of the existence of a total heart block.

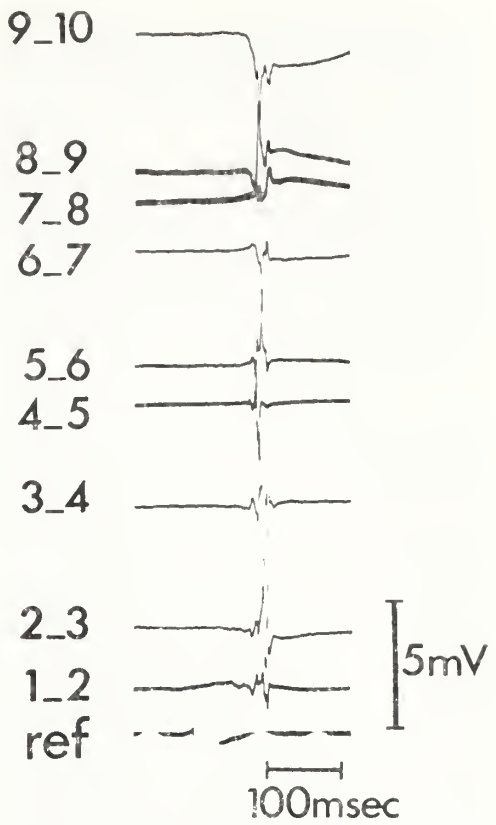

FIG. 13. Bipolar complexes from regions with fibrous tissue in the human heart showing the notching of the intra-infarction complexes as found in the dog's heart.

trodes result from the existence of multiple small excitatory waves in that area (Fig. 11). These fragmentary excitatory waves are constant from beat to beat, and are asynchronous.

HUMAN MYOCARDIAL INFARCTION

Are these changes present as well in the human heart with an old infarction?

We had the opportunity of studying some aspects of excitation in a human heart, revived about 1½ hours after death. About twenty intramural electrodes were introduced, but I can give you only some of the results, because the correlation of the many electric and anatomic data is still in progress. The physiological condition of the heart was satisfactory, because after 5 hours of perfusion the membrane potential was still 82 mV. In a normal hypertrophic part of the ventricular wall we found regular outward spread in the outer layers, but nearly synchronous activation in the middle and inner layers (Fig. 12). Reversals, undistinguishable from those found in the dog's heart, were present. In comparison with the normal human ventricular wall, there appears to be an increase in synchronously activated layers. It is not possible to give an explanation for this phenomenon. The anatomy of that part of the wall in which the intramural electrode was situated, indicates that such reversal was not caused by

the trabeculated structure of the inner layers. A complete A.V. block was present, however, with grossly abnormal excitation of the ventricular walls, probably occurring mainly in a tangential direction.

A large fresh postero-septal infarction and an older scar were present and some of the intramural electrodes were situated in the latter region. The same highly notched complexes as found in scars in the dog's heart were recorded (Fig. 13).

Precordial Complexes

One can now ask a very important question: are these small and fast deflections detectable at the precordium? This question can be answered affirmatively for the dog with an old infarction. They could be demonstrated in some of the cases explored. Comparing epicardial and precordial complexes, one can see, however, the loss of important details, due to the greater distance of the precordial electrode. This fact has to be accepted, because it cannot be changed. But it is evident, that a second cause for loss of information is man-made: the use of recording machines without high-frequency response, an inadequate recording technique. The improvement in diagnosis which can be obtained by using high fidelity recording techniques is great, as shown by Langner's *et al.* pioneering work. He proved that small and fast deflections may be present at the human precordium, a fact of the greatest clinical importance, because it points to one of the ways for a better and more rational electrocardiographical diagnosis.

Another one will be the development of lead systems which can detect better the proximity effects of excitation in precordial leads. But still more will be gained if electrocardiography is placed on its proper foundation, namely the study of total excitation of the human heart in normal and abnormal conditions. Findings from such studies must then be correlated with a careful analysis of the anatomic structure using histochemical and even biochemical methods. Through the cooperation of several disciplines we must unravel the mysteries of the dead organ, brought to life again. This is what Claude Bernard had in mind when he coined the term: "autopsie physiologique", a possibility now within our reach, and this I hope I have demonstrated for you today.

Acknowledgments

My sincere thanks are due to Drs. Büller, Van Dam, Freud, Van Lier, Meijler and Roos.

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The help of Dr. Raymond D. Pruitt in the preparation of this paper is gratefully acknowledged.

Drug Antigens and the Diseases Which They Produce[1]

By MAX SAMTER, M.D.[2]

YOUR invitation to present the Hira S. Chouké Lecture of The College of Physicians of Philadelphia, honors and moves me very much. It moves me because of the wording of the letter in which Dr. Kehar S. Chouké established this lectureship in memory of his father who 'was gentle and went out of his way to do things for others', and who suffered, most of his life, 'from migraine headaches and some unknown allergy.' I am very grateful to you.

It would be hybris to pretend that the unknown has yielded to our curiosity and inventiveness. But it is reassuring that the awareness of uncertainties in the area of applied immunology which I shall try to outline, this evening, has at least produced a blueprint which clarifies the direction of future search and future advances.

Introduction: the Nature of Drugs

The subject of this review sounds deceptively simple. Unfortunately, however, drug-antigens are not born, but made; and the road toward an understanding of the antigenicity of drugs is tortuous and beset with obstacles. When I read the first draft of this paper, it surprised me: it describes its destination rather briefly, and spends most of its effort and emphasis on describing the difficulties in getting there.

It might be well to begin with a definition: a drug is a chemical which—whatever the reason for which it has been taken—produces a pharmacological effect. Antibiotics are drugs, and aspirin is a drug, but so are insecticides which have been inhaled, preservatives and coloring matter of food that has been eaten, or cosmetics which have been placed on the skin. Alice in Wonderland took a drug when the Caterpillar teased her into eating the mushroom: "One side will make you grow taller, and the other side will make you grow shorter."

"One side of what? The other side of what?", thought Alice to herself. "Of the mushroom", said the Caterpillar, just as if she had asked it aloud, and in another moment it was out of sight.

Alice remained looking thoughtfully at the mushroom for a minute, trying to make out which were the two sides of it; and, as it was perfectly round, she found this a very difficult question. However, at last she stretched her arms around it as far as they would go, and broke off a bit of the edge with each hand.

"And now which is which?", she said to herself, and nibbled a little of the right-hand bit to try the effect.—and like Hofmann who—in 1943—synthesized LSD and, at the end of the day, tasted a mere trace of the powder, Alice learned by experience. Hofmann, on the way home, became aware of his rapidly developing psychosis, and recorded it—a classic in Medicine. Alice shrunk and grew; and we are still here wondering as she did: 'which is which?'

Between Absorption and Excretion: the Fate of Drugs

In a delightful and informative paper, Brodie (1) (who has made outstanding contributions to the study of distribution and fate of drugs) indicates that man and animals are capable of excreting lipid-insoluble substances effectively. Differences appear when experimental animals are exposed to lipid-soluble compounds—hydrocarbons, terpenes, alkaloids, steroids—which cannot be excreted, unless they are modified. The capacity of any species to handle chemicals, might well depend on its phylo-

[1] Hira S. Chouké Lecture VI, The College of Physicians of Philadelphia, 13 October 1965.

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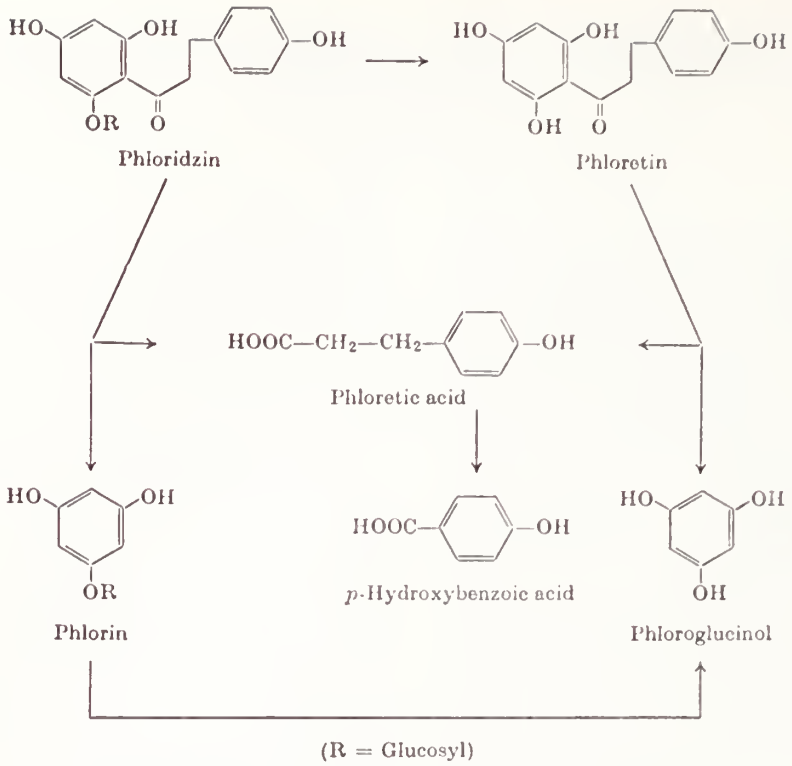


Fig. 1. Metabolism of phlorhizin and phloretin. (species: Malus)

genetic past; soil bacteria and man, for instance, appear to metabolize phloridzin and phloretin, products of the apple tree, with comparative ease. (2) (Fig. 1)

Lipid-soluble drugs must be made less lipid-soluble to permit adequate excretion: this, and this alone is the objective of drug-metabolizing enzymes. The process—the 'polarization' of lipid-soluble compounds—requires two operations, (1) the mobilization of oxidative enzymes which catalyse the formation of hydroxyl or amino groups and (2) the conjugation of these newly created groups to substances of low lipid-solubility. The polarizing enzymes are stored in the microsomes of the liver which have a selective lipoid barrier for the protection of 'normal' substrates. (Fig. 2).

Williams' (3) comprehensive text on the metabolic disposal of drugs is called: 'Detoxication Mechanisms', but Brodie prefers the term: polarization, since metabolites, while less lipid-soluble, might, in fact, be more active, more toxic than the parent compound Brodie himself has studied the biotransformation of phenylbutazone which yields a potent anti-inflammatory (oxyphenbutazone) as well as a potent uricolytic agent, the precursor of sulphinpyrazole. Yet, even though we are much more sophisticated than we used to be, biotransformation is, more often than not, unpredictable. The resemblance, for instance, of the three sedatives which are included in figure II is startling, but phenobarbital and glutethimide appear to be safe, while thalidomide—given during a comparatively brief, but critical period of pregnancy: from the fourth to the seventh week—has produced severe malformations in at least twenty percent of human offspring; and, to a lesser, but still significant extent in other mammalian embryos. The mechanism by which the injury occurs, is still uncertain; increasing evidence suggests that thalidomide is converted, in vivo, into an active derivative, possibly into an antimetabolite,

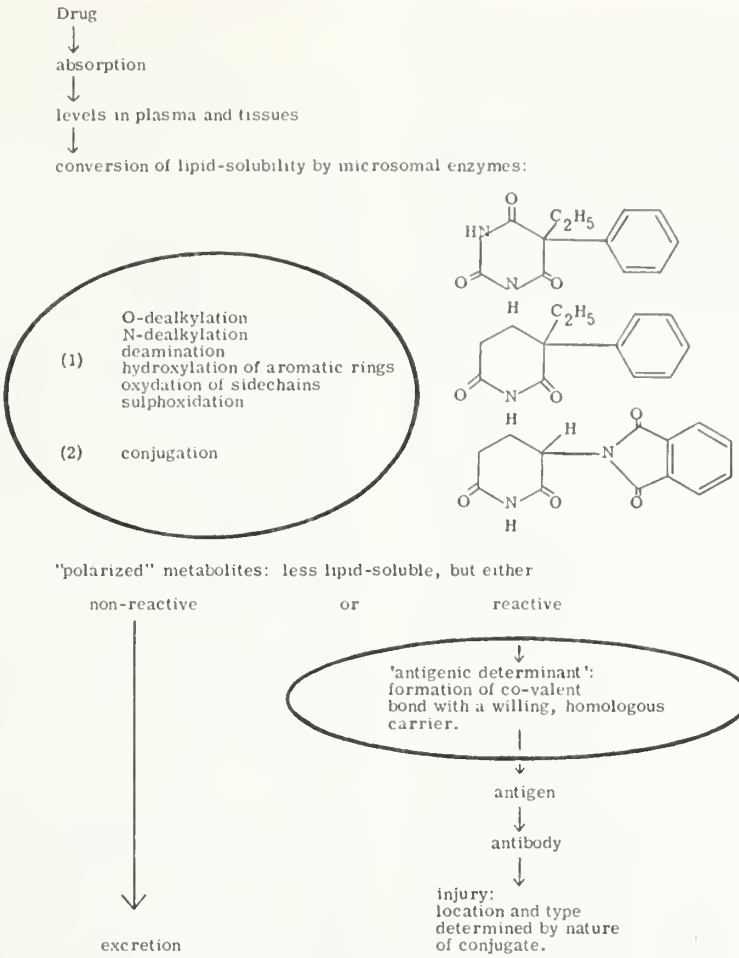


FIG. 2. Enzymatic handling of lipid soluble drugs. Compounds on the right in the order listed: phenobarbital, glutethimide, thalidomide.

which damages the fetus, but there is as yet no final answer.

THE ACTION OF ENZYMES ON DRUGS, AND OF DRUGS ON ENZYMES

The few experiences which occurred while we watched—the world-wide catastrophe of thalidomide, the limited catastrophes of the monoaminooxidase inhibitor tranylcypromine—have raised the question whether our tendency to prescribe more and more drugs, should be expected to produce more and more reactions. Simple logic seems to favor an unqualified 'yes', but simple logic has not counted on the ingenious behavior of microsomes. Certainly, if two drugs compete for the same substrate, the demand might exceed the supply: fortunately, alternate pathways might exist. In the absence of alternate pathways, lack of the conjugating enzyme—e.g. the absence of glucuronyl transferase in the newborn—might be critical if drugs are given which, like chloramphenicol, are excreted as glucuronides. Drugs might inhibit enzymes—monoaminooxidase inhibitors, as I have mentioned, might not only act on the pressor amines of the brain, but prevent the destruction of gastro-intestinal tyramine. Strangely enough, however, drugs might not only stimulate the metabolism of those enzymes which inactivate them, but of other en-

zymes which inactivate other drugs: phenobarbital (to name a striking example) shortens the half-life of certain anticoagulants.

An elegant demonstration of the effect of various drugs on a single enzyme has been developed by Wattenberg (4) at the University of Minnesota. Wattenberg worked with the carcinogen, benzpyrene, which is converted by gastro-intestinal benzpyrene hydroxylase into the comparatively innocuous metabolite, hydroxy-benzpyrene. Wattenberg was able to demonstrate that administration of benzpyrene induces increased enzymatic activity, but that a comparable increase could be induced by a number of drugs, e.g. by some of the phenothiazines, and by flavones. It had been my intention to present two of Wattenberg's slides, but the duplicates, unfortunately, did not arrive in time. The implications of Wattenberg's studies are rather exciting. The effect of such stimulation might be harmful or beneficial, but differs, of course, for each individual combination of drugs—only a handful of the thousands of possible groupings have been studied, so far. Progress has been slow, mainly because the evolution of our experimental animals differs so much from our own: the species which we happen to choose might either lack the specific enzymes with which we are concerned; or even if it harbors the enzymes, might not use them in accordance with expectations. To compound the confusion, the faulty animal might actually *form* the metabolite under study, but might dispose of it in a phylogenetically appropriate, but wholly unforeseeable and inhuman fashion: fish, I regret to say, simply excrete lipoid-soluble compounds through their gills. The genetic differences in strains of animals and in men have been examined with considerable care: the hydrolysis of succinylcholine by pseudocholinesterase, the defect in glucose-6-phosphate dehydrogenase which leads to primaquine sensitivity, the defects in acetylase which permit a separation of into slow and rapid inactivators of isoniacid are a few examples of the rapidly growing field of pharmacogenetics. (5).

The Classification of Drug-Induced Allergic Disease

Until now, this review has discussed the formation of active, and perhaps toxic metabolites, but has carefully avoided the use of the crucial terms: 'hapten' and 'antigenic determinant' which apply when the action of enzymes on a drug permit one or more of its fragments to enter a stable union with components of tissue. Such fragments may shed or retain their toxicity, as they become antigens and initiate the immunological sequence which will, eventually, become a disease.

Modell, (6) in a recent review of drug-induced diseases, deplores the tower of Babel which complicates scientific communication. He feels that the term 'adverse effects' lacks specificity and might include, for instance, our confrontation with the problems of old age which is clearly the result of the effective use of drugs. 'Toxic effects' are consequences of the pharmacological actions of drugs or chemicals—and are quite often coupled with their therapeutic activity. 'Intolerance' designates expected pharmacological reactions produced by unexpectedly small doses of a drug; 'idiosyncrasy' unexpected and unusual pharmacological reactions, e.g. excitement after barbiturate. 'Allergic reactions' require the presence of an antibody and, therefore, unlike toxic reactions, previous exposure or, as it were, an incubation time. The term 'side effect' is too broad to have *any* meaning.

Modell favors a re-classification based on the physiological system with which drugs interfere when they cause disease. Consequently, he proposes to classify diseases caused by drugs (1) which act on defense mechanisms; (2) produce cell injury; (3) result in an imbalance of essential components of physiological regulations, i.e. enzymes, hormones, electrolytes; (4) engender abnormalities in the fetus; (5) lead to carcinogenesis and (6) alter microbial ecology. In Modell's scheme, drugs which become antigens are drugs, then, which modify the defense mechanism of the species.

'Antigenic Determinants' in Experimental Animals, and in Man

It is comparatively simple to design a 'hapten', conjugate it in vitro with a suitable macromolecular carrier, and induce sensitization in experimental animals. Landsteiner, Eisen, Parker, and their associates (7, 8, 9) have clarified the conditions which must be met, before simple chemicals become 'antigenic determinants'. It has been established, for instance, that reversible binding—e.g. the binding of dyes or salicylates to circulating serum albumin—is not sufficient to induce antibody formation: it is necessary to form a covalent bond between the simple chemical and the amino acid residues of the macromolecular carrier to which it is attached. The attachment which is nonionic and stable tends to modify the structure of the 'hapten' which becomes an integral part of the conjugate and cannot be separated from the carrier by conventional physico-chemical procedures. Of common haptens, the studies of penicillin have been most extensive and fruitful.

While the same experimental principles, we believe, govern the emergence of drug-antigens in man, the clear and precise sequence of the controlled experiment is usually absent in drug-induced allergic disease. In many instances, we are not aware of the nature of the drug; and even if the drug is known to us, the nature of the metabolites tends to be obscure and uncertain. Penicillin, for instance, has been investigated so intensively that we should understand the sequence of metabolic transformation which produces covalent conjugates and subsequent reactions, but even in this comparatively 'settled' area it now appears that it might not be the drug itself, but its "minor contaminants" which encourage the formation of conjugates and antibodies.

The formation of haptens (and the prevention of it) must be considered the focal point for any attempt to prevent allergic reactions to drugs. The hapten, however, is not yet an antigen: it has to find a willing protein with which it can conjugate. It is likely that the body frowns upon the formation of conjugates and that auxiliary factors are needed to accomplish conjugation. Infection appears to offer an easier access to the amino acid residues, e.g. to lysine, or cysteine: consequently, infections increase the incidence of drug reactions.

The newly-formed antigen might "sensitize" but the type of sensitization is not predictable. Years ago, the literature seemed to indicate that conjugates of small chemicals with protein will induce allergies of the "immediate" type characterized by the explosive release of chemical mediators, while antigenic determinants conjugated to lipoids, e.g., to the wax fraction D of the tubercle bacillus, would produce delayed sensitivity and, subsequently, accumulation of lymphocytes and inflammation at the site of exposure. Unfortunately, the simple concepts are no longer valid in the light of our more advanced immunochemical techniques. Modell (in the review which I have previously cited (6)) states that the hapten, rather than the protein moiety, accounts for the 'specificity' of the allergic reaction: this statement, however, is open to debate. It is my impression that the macromolecular carrier rather than the hapten might determine site and type of the allergic disease. A chemical which attaches itself to platelets, might readily induce an antiplatelet antibody, but a hapten which combines with components of the vascular bed, might induce generalized periarteritis.

The antigenic conjugate which is, indeed, a *prerequisite* for sensitization, does not necessarily induce antibody formation in every species, or even in every individual of a species with a known capacity to respond. We have previously mentioned the genetic pattern of enzyme activity which distinguishes species from species, individual from individual: it is virtually certain that genetic factors also control the response of the mesenchymal tissue to antigenic challenge. Mice, guinea pigs, rabbits and even primates might contribute solid bits of immunological information, but are unlikely to solve the mystery of drug reactions in man.

Comparative Specificity of Hypersensitivity to Drugs

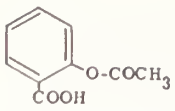
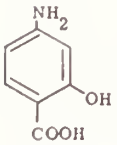
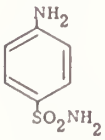
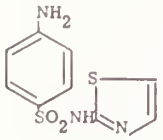
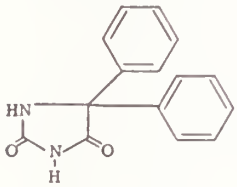
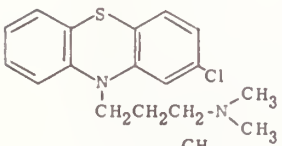
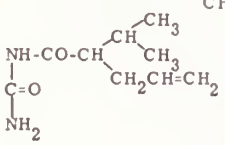
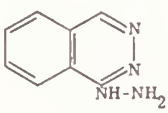
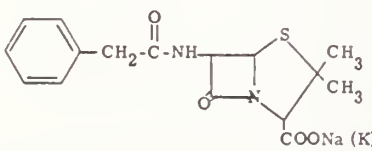
Drug:	Type of Reaction	Tissue injury
	uncertain: possibly cholinergic	rhinitis and bronchial asthma; angioneurotic edema
	vascular	granuloma (liver: jaundice) exfoliative dermatitis formation of 'virocytes'
	vascular	granuloma (liver: jaundice) exfoliative dermatitis no virocytes
	vascular	periarteritis nodosa
	'serum sickness', 'lymphadenopathy', erythema, vesiculation	Stevens-Johnson syndrome
	intrahepatic cholestasis; eosinophilia, photosensitivity	jaundice; erythema
	anti-platelet-antibodies	thrombocytopenia
	anti-DNA-antibodies	systemic lupus erythematosus
	anaphylaxis	acute rhinitis, bronchial asthma, angioneurotic edema, shock; 'serum sickness'

FIG. 3. Drug-antigens and the diseases which they produce. Drugs in the order listed from left to right:

acetylsalicylic acid
p-aminosalicylic acid
sulfanilamide
sulfathiazole
diphenylhydantoin
chlorpromazine
allylisopropylacetylcarbamide
hydralazine
benzyl-penicillin

I am reminded of Davies (10) who concluded a similar symposium on drug reaction with an expression of hope that some day, we might be able to say, again like Alice: "Come, that finishes the guinea pigs. Now we shall get on better."

Signs and Symptoms of Drug-Derived Allergic Disease

Drug-induced allergic diseases in man occur in an infinite variety which is probably due to strong affinities of active metabolites to specific macromolecular carriers or tissues (11). Fig. 3 presents a number of drugs which are widely used, and lists the major syndrome for which they are known even though one realizes that each drug might, on occasion, cause another set of reactions and that each syndrome might be caused by another set of drugs. You will readily identify the photographs: the angioneurotic edema which follows ingestion of acetylsalicylic acid;* the p-aminosalicylic acid reaction which simulates infectious mononucleosis; the sulfanilamide—induced granuloma which might be associated with jaundice and exfoliative dermatitis, but not with atypical lymphocytes; periarteritis nodosa caused by sulfathiazole which is now obsolete; Stevens-Johnson syndrome traced to diphenylhydantoin; chlorpromazine jaundice, and photosensitivity after chlorpromazine; 'Sedormid'—purpura; systemic lupus erythematosus of hydralazine—treated patients which usually, but not always, disappears when the drug is withdrawn; and the ubiquitous anaphylaxis and serum sickness which are associated with penicillin therapy. It is obvious that, at this time, these symptoms defy our inclination to interpret them in classical and established immunological terms. The late Richard Jaffé—eminent pathologist of Cook County Hospital on Chicago's West Side—used to say that we have succeeded in inventing neat compartments for every conceivable disease, but that nature, willful and uncooperative, appears to be inclined to disregard them.

* The classification of aspirin as a possibly cholinergic drug is unorthodox, but we have reason to believe that acetylsalicylic acid might act, in aspirin-sensitive patients, on cholinergic receptors. Moreover, if acetylsalicylic acid were a hapten, where would it conjugate?

Speculations About the Future

It is my guess that the presentation of this catalogue of metabolic and immunological transformations which precede drug-induced disease in man, must convey to you the same feeling of ambiguity and wonder which I have felt for some time: first, that drug-induced diseases are not more common than they are; and second, in view of the complexity of the process, that they occur at all. In addition, it seems likely that you will ask: where do we go from here? and, perhaps, like the 'new' mathematics of our children, the 'new' immunology might provide an answer. The early phase of drug-induced disease will remain unchanged: metabolites must find homologous carriers. It might be helpful, on the other hand, to take a second look at the conjugate which, at this moment, is still an alien in an hostile homologous setting, in search of an antibody which might destroy it. It has become an almost inescapable conclusion that *macrophages* participate, as intermediates, in antibody formation: there is good reason to believe that the attraction of macrophages is one of the essential virtues of Freund's adjuvant. Several possibilities are under scrutiny: macrophages might take up antigen, protect or degrade it, produce messenger-RNA which transmits coded information, or combine messenger-RNA with antigenic determinants which—after transfer across cellular membranes—induce antibody synthesis in appropriate lymphocytes. Fig. 4 illustrates, in conscious simplification, two possibilities for such a transfer. Studies, to date, have been carried out with bacterial antigens, bacteriophage, heterologous protein, I^{131}-hemocyanin, (12, 13) and, while far from conclusive, should provide a unique experimental tool for the study of drug-derived antigens which permit, as a rule, intracellular identification. At this junction, macrophages are one of our brighter hopes, a happy dream of

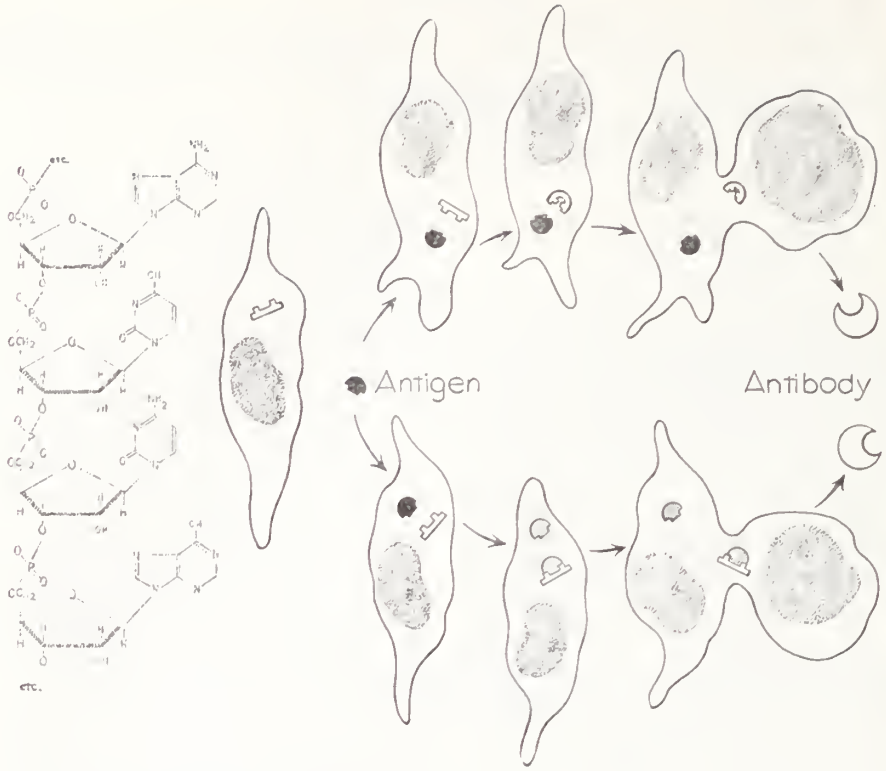


FIG. 4. Proposed scheme for the transfer of messenger-RNA from macrophages

investigators who seem to be confident that macrophages might provide a key to the riddle why drug-antigens induce sensitization in some patients, but not in others. If they are right, we might learn to manipulate macrophages, and prefer their manipulation to the manipulation of drugs. The problem of drug-antigens, then, will no longer be a problem of selecting the proper drug, but of anticipating the response of the host; and of adapting it so effectively that metabolites and haptens do not represent a regrettable and often embarassing complication, but an essential part of a planned therapeutic regimen.

While the prospect of such a host-centered approach today, still has all the elements of wishful thinking, the problem itself, the attempt to shift our concern from drug to man, is old. When Paracelsus in 1537 was attacked for his 'new prescriptions', he blamed in his "Seven Arguments", those "ignorant, opinionated quacks, who claim that the prescription I write is poisonous, a corrosive, and the essence of every evil poison in nature. My first reply to such sham pretense and clamor," he continued, "would be to ask if they know what is poison and what is not poison? Or is not a poison one of the mysteries of nature? For on these very points they lack knowledge and understanding of nature's forces. For what thing is there, created by God, which is not endowed with some great gift for the good of mankind? Why then should poisons be thrown aside and despised when it is not the poison, but nature that is being tried?" (14). Whatever then our predicament in the handling of drug-antigens and the diseases which they produce, we are, indeed, in exalted company.

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The Central Lymphoid Tissue in Developmental Immunobiology[1,2]

By ROBERT A. GOOD,[3] M.D., ANN E. GABRIELSEN, M.A., RAYMOND D. A. PETERSON, M.D.,[4] AND MAX D. COOPER, M.D.[5]

DURING the past four or five years we have, after literally centuries of speculation and many decades of investigative effort, come to at least a first understanding of thymus function in the development and sustenance of the lymphoid tissues and their immunologic function. One of the by-products of this growth of knowledge about and research on the thymus has been an interest in the "thymicologists" of the past whose conclusions and intuitions are so contemporary in flavor. William Hewson, an 18th century physician, viewed the thymus as a source of cells distributed to the circulation and to other tissues, cells that he observed with little more than a good hand lens (1). A century later, John Beard, an English anatomist, was strenuously arguing the thesis that the other lymphoid tissues of the body (his major experiments were done in rays) derive from the thymus, the tissue in which "leucocytes" first develop and which functions as the parent source of all the "leucocytes" which "colonize" the other tissues (2). This was an unpopular view at the time and has been an unpopular view down to our own time; but we feel now that he was at least partly right.

Another major figure in thymus research, to whom we clinicians in particular owe an enormous debt, is J. August Hammar, the Swedish scholar whose researches on thymus size and weight (3) ultimately resulted in repudiation of the concept of status thymicolymphaticus, accepted for many years as a clinical entity, and long used as a diagnostic basis for radiation therapy to reduce thymic size in children.

There have been many others, of course, down to such contemporaries as Jacob Furth, who, with McEndy and Boon (4), first firmly linked the thymus to leukemia in mice by thymectomizing animals of the high-leukemia strain Ak and preventing the disease. However, the recent immunologic research stemmed in large part from some discoveries regarding immunologic function in chickens and its dependence on the bursa of Fabricius, particularly the work of Glick and his associates (5), and of the Wisconsin group headed by the late Harold Wolfe (6).

Central Lymphoid Tissue

It has become increasingly difficult to consider the thymus alone in discussing the ontogenesis of adaptive immunologic processes; we have, therefore, adopted the term "central lymphoid tissue" to designate a class of lymphoid tissues of which the thymus is the prototype. We have not yet identified all the central lymphoid tissues, nor have we entirely defined their essential characteristics and roles. Present evidence suggests that they all arise from or in close association with the epithelium of the gastrointestinal tract; that they are sources of cells to the periphery (7), as suggested by Hewson and Beard; that they elaborate and secrete hormones which influence lymphoid tissue development and/or immunologic competence (8, 9); that they are relatively secluded from

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[5] Postdoctoral Fellow, U. S. Public Health Service.

active immunologic processes (10); but that they govern the structural and functional maturation of the "peripheral lymphoid tissues" (11–13). Most clearly "peripheral lymphoid tissues" are the spleen and lymph nodes; they are derivative in ontogenesis, dependent on the central lymphoid tissue in early life, although relatively autonomous later. By and large they are the effectors of immune responses: they have immunologically competent components of both lymphoid systems.

Best defined as central lymphoid tissues are the thymus and the bursa of Fabricius (5, 6, 11–13). The appendix of the rabbit—or perhaps only a portion of that organ—seems to have this type of function in postnatal life (14). Clearly there are others: we have not yet found the mammalian equivalent of the bursa of Fabricius, for example. Also the small-lymphocyte type of development in the rabbit seems to be dependent on still another tissue in addition to the thymus itself and the appendix.

It is only during the last year that a second type of organization of the lymphoid system—long implicit in clinical and experimental observations—has been clarified experimentally. What has traditionally been considered "cellular" immunity: homograft rejection, graft versus host reactivity, and responses of the delayed hypersensitivity type—are functions of the thymus-dependent lymphoid system which consists largely of small lymphocytes (11–13, 15, 16). Germinal centers, plasma cells, and immunoglobulin production are dependent on the bursa of Fabricius in chickens (15, 16) and on an as-yet-unidentified central lymphoid tissue in mammals. All indications are that specific antibody production is a function of interaction of the two systems, the thymus-dependent cells probably providing a recognition-information component for the immunoglobulin-production system of germinal centers and plasma cells.

Since the bursa of Fabricius was the first central lymphoid tissue to be defined, and since the delineation of the two lymphoid systems was achieved in the chicken, we should like to present a brief account of these developments, followed by a statement of the clinical implications and appications as we see them at the present time.

Ontogenesis of Adaptive Immunity in the Chicken

For centuries the avian bursa of Fabricius, named after the great 16th century anatomist, had remained as mysterious as the mammalian thymus, serving no discernible function. It involuted rapidly at the onset of sexual maturity; earlier extirpation seemed to have little effect on the animal, including its immunologic function. The key finding was that of Glick, Chang, and associates (5): that antibody production to Salmonella typhimurium was greatly curtailed in chickens bursectomized surgically in the early post-hatching period. The crucial factor was the *age* of the experimental animal, as it proved to be in the later thymus work. The Wolfe group at Wisconsin confirmed the effects of early bursectomy with other antigens, and also extended these experiments to chickens whose bursa development had been arrested during incubation by administration of 19-nortestosterone (6).

The earliest tendency was to think of the bursa as the avian equivalent of the thymus, although the chicken also has a cervical thymus; a major transition came in 1962 when the concept of dissociation of immunologic function in the chicken was proposed by Warner and Szenberg (17). These investigators were also working with a hormonal bursectomy model in White Leghorns; but they found that some of their birds had complete atrophy of the thymus as well as arrest of bursal development, and that the immunologic status of this group differed significantly from that of birds with an undeveloped bursa but a relatively normal thymus. The dissociation that they proposed was this: that antibody production and delayed hypersensitivity are dependent on the bursa; that homograft immunity is dependent on the thymus; and that the cell system responsible for graft versus host activity is not clearly dependent on either tissue.

This formulation had many difficulties: it

ran counter to a great deal of clinical and experimental evidence on so-called cellular and humoral immunity; and it was based on a technique which probably had variable effects on the thymus which were not assessable except perhaps at the extremes.

Evidence that the concept of dissociation, if not the details of the Warner-Szenberg division, was probably valid was not long in coming. Aspinall *et al.* (18) found some prolongation of skin homograft survival in surgically thymectomized chickens; Jankovic and his associates (19), in Yugoslavia, presented evidence that surgical thymectomy affected responses of the delayed hypersensitivity type, while surgical bursectomy did not; Peterson *et al.* (20) found that bursectomy and not thymectomy greatly reduced the incidence of visceral lymphomatosis, the major lymphoid malignancy of chickens; and Ortega and Der (21) found that complete bursectomy of newly hatched chickens consistently produced 7S agammaglobulinemia in the maturing animals. When considered in the light of the immunologic disability in neonatally thymectomized mice, rats, and hamsters: a primary failure of transplantation immunity, graft versus host capability, and delayed allergy (see 11–13, 22–24); and in the light of clinical syndromes such as the Bruton type of agammaglobulinemia (25), in which cellular immunity is relatively intact but immunoglobulin producing capability almost nonexistent (see 26), the chicken data suggested that avian thymus probably has the same type of function as the mammalian thymus, and that the bursa governs the ontogenetic development of capacity for immunoglobulin production.

The crucial experiments by Cooper *et al.* (15, 16) involved the addition of heavy irradiation to surgical bursectomy or thymectomy in the newly hatched period. The thymectomized-irradiated chickens had defective homograft responses, poor graft versus host activity, and deficient reactivity of the delayed hypersensitivity type. As in neonatally thymectomized rodents, antibody production was also deficient. Most striking were the findings in the bursectomized-irradiated chickens; these birds were both 19S and 7S agammaglobulinemic, and produced no antibody despite repeated stimulation with potent antigens, with and without adjuvants. They rejected homografts, though more slowly than normal, and had relatively normal graft versus host capability.

The histologic abnormalities of the lymphoid tissues of these two groups were very different, and enabled Cooper *et al.* (15, 16) to define the cellular components of the thymus-dependent and the bursa-dependent development. The thymectomized-irradiated birds had low circulating lymphocytes and very few small lymphocytes in the white pulp of the spleen and in other tissues. The germinal centers seemed to be intact and plasma cells were evident. On the other hand, the bursectomized-irradiated chickens had no germinal centers and no plasma cells, an entirely consistent finding section after section, bird after bird. Small lymphocytes were seen in normal numbers in the tissues, and circulating lymphocyte levels were normal in these animals.

Thus, we had both a functional and a morphologic division of lymphoid development in the chicken. All indications are that this same kind of division prevails in mammals: the parallels in thymic system function are close. Although we are not yet able to manipulate the immunoglobulin-producing system in mammals, because we have not yet found the bursa equivalent, the clinical existence of a group of patients with virtually the same morphologic and immunologic deficit as bursectomized-irradiated chickens argues strongly for the existence of such a tissue or tissues. Sex-linked recessive agammaglobulinemia is the syndrome in which cellular immunity is relatively intact but immunoglobulin and antibody production almost nonexistent. The well defined pattern of inheritance provides a strong argument for the existence of the two systems in man, each determined by separate genes presumably controlling central lymphoid tissue development.

Clinical Immunologic Deficiency and the Two Systems View

In our laboratory, clinical immunologic deficiency has been a major concern for a decade or more; one of these patients provided the first impetus toward our study of the thymus. Many others have influenced experiments or, in reverse direction, provided clinical reinforcement of conclusions reached in the laboratory.

We recently documented in detail our current view of the various immunologic deficiency diseases in the light of the recent experimental findings on the role of the thymus and the bursa of Fabricius (27). Three are most relevant to the experimental immunologic deficiencies described in the preceding section. Sex-linked recessive agammaglobulinemia resembles very closely the defect of bursectomized-irradiated chickens. The closest clinical analog to thymectomized-irradiated chickens and neonatally thymectomized rodents known to us is an extreme congenital lymphopenia, occurring in the presence of relatively normal immunoglobulin and plasma cell development (28, 29). Thymic alymphoplasia is characteristic of these children. The third and most extreme clinical immunologic deficit is the Swiss type of agammaglobulinemia, in which neither system develops: the children have an extreme deficit of both plasma cells and lymphocytes. Thymectomized - bursectomized - irradiated chickens approach this deficit; however, we have not been able experimentally to reduce the thymus system to the minimal level of these patients. Classic Swiss agammaglobulinemia (see 27) is inherited as a simple autosomal recessive trait; we believe that it involves an earlier arrest of differentiation of both cell systems, before they diverge. The thymic development in this disease is characteristically more primitive than in the other lymphopenic syndromes: very small, lacking all lymphoid development, and located in an undescended position high in the chest.

One of the most enigmatic of the immunologic deficiencies, extraordinarily variable in expression, is that associated with ataxia telangiectasia. For some years it was evident that this syndrome, characterized primarily by a progressive cerebellar ataxia and telangiectases of the sclera, eyelids, and ear lobes, usually involved inordinate susceptibility to sinopulmonary infections (see 30). A few of the patients were hypogammaglobulinemic, but most had normal gamma globulin levels; however, beginning with the patients of Thieffry *et al.* (31), a number of cases with a deficiency of the gamma^A immunoglobulin were noted. Most remarkably, back in 1958, Boder and Sedgwick (30) had reported a case in which no thymic tissue was found at post-mortem. With more directed study—of the immunoglobulins, of immunologic responsiveness, including antibody production, delayed allergy, and transplantation immunity, and of thymic tissue at autopsy or biopsy—a pattern began to emerge. While there is a good deal of variability from case to case, many of the patients studied have had a low titer of gamma^A globulin, deficient transplantation immunity, poor antibody response to such antigens as actinophage, and either no detectable thymus or a small, histologically abnormal thymus (see 32). Some of the children are severely lymphopenic. In additon to the threat of infection, many of these patients are unusually vulnerable to lymphoid or reticular malignancies. Since ataxia-telangiectasia has an established pattern of inheritance, as a simple autosomal recessive, we know that this rare, obscure disease is offering us unusual insights into thymic function, immunologic defect, and oncogenesis.

A patient with acquired agammaglobulinemia and a thymoma first brought us to consider a possible immunologic role for the thymus (33). This patient's disease, characterized initially by repeated bouts of pneumonia, had its onset at about the same time as a large thymic tumor. The tumor was removed without affecting the immunologic deficit. Oddly enough, despite the advances in knowledge of the thymus clinically, this association of thymic tumor and agammaglobulinemia remains

obscure. There has been a great increase in the number of reports of this association in recent years, to a total of at least 18 or 20 cases. It may well be that the tumor is a consequence of the immunologic deficiency, perhaps reflecting compensatory activity on the part of the thymus.

We have known for several years that primary or idiopathic "acquired" agammaglobulinemic patients are a disparate group: their other hematologic abnormalities range from aplastic anemia, eosinopenia, isolated neutropenia, to pancytopenia; and while some have small, atrophied lymphoid tissues, others have hypersplenism and hyperplastic nodes suggesting follicular lymphoblastoma (see 26). This latter group has been of particular interest recently: the morphologic definition of the immunoglobulin producing system, noted earlier, makes it clear that this patient group has disease of the immunoglobulin producing system. Many of their germinal centers look very much like those found in the spleen and pancreas of chickens early in the course of visceral lymphomatosis. One of our own patients had this type of history: follicular hyperplasia of the lymph nodes, hypersplenism, and onset of extreme hypogammaglobulinemia at the age of 22. Her close relatives include several persons with severe rheumatoid disease; she herself has a moderate arthritis (26). According to her history, she had had enlarged tonsils which all but disappeared at the onset of her disease (27). If the tonsils are the, or one of the, central lymphoid tissues comparable to the avian bursa, it may be that both peripheral disease of the immunoglobulin producing system and failure of central lymphoid tissue function are necessary to cause agammaglobulinemia. We hope that further experiments in chickens developing visceral lymphomatosis may shed further light on this clinical problem.

One of the questions that is receiving a good deal of attention in our laboratories is that of the two systems view in relation to malignancy of the lymphoreticular tissues. The two best studied experimental lymphomas, the classical thymus-dependent leukemia of mice (4) and visceral lymphomatosis of chickens (20), seem to involve only one of the two lymphoid systems, and, in their early stages, are manipulable by removal of the appropriate central lymphoid tissue. We are only beginning to consider whether initial involvement of one of the lymphoid tissue components may not be common to lymphocytic malignancies in general, including those of man.

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Mental Health

Community Care in Britain?[1]

By HENRY R. ROLLIN, M.D., D.P.M.[2]

LIES, damned lies and statistics! This antique saw still has teeth, and never so sharp, I think, as when used on medical matters. Whether this is due to mathematical unsophistication, or political naiveté, or both, on the part of doctors—in Britain at any rate—I don't know. Take, for example, the findings of the Willink Committee in 1957. This body composed of eminent gentlemen, medical and lay, and chaired by a former Minister of Health, announced that on the evidence laid before it, the British Medical Schools were over-producing doctors at the rate of 10% per year. By what miracles of mathematical manipulation this decision was arrived at only the said gentlemen can give the clue. But for my hard-pressed colleagues and myself who could be easily persuaded that slide-rules were the instruments governing the Cresta Run this was arrant nonsense. With an exploding population at home and in the countries to which Britain traditionally exported doctors, how could these findings possibly be valid? For the politicians, however, this was a Heaven-sent opportunity to economise, and with indecent haste measures to cut down the entries to the schools and their teaching staffs were put into effect. All too soon the desperate shortage of doctors, greater indeed than would have obtained even if the cuts had not been made seriously embarrassed the profession and imperilled the entire National Health Service. Only when the situation became critical was a mistake admitted and steps taken to restore the status quo. But it is infinitely more difficult to build up a school and its staff of teachers than to destroy one.

Take another example, one more pertinent to our present theme. The year 1961 was according to some, an annus mirabilis in the history of British psychiatry. In that year three papers were published, their almost simultaneous appearance being, as far as I am aware, entirely fortuitous. All three were forecasts, based on statistical analyses of current trends, of the future needs of British Mental Hospitals in terms of beds; and what was surprising was the high degree of accord in the conclusions of the different authors. Dr. G. C. Tooth and Miss E. N. Brook (1961) found that in planning for the future there is likely to be a need for 1.8 beds per thousand of the population instead of the present 3.4 per thousand, that is, a drop of approximately one half. K. W. Cross and Janet Yates (1961) in a regional study in the Birmingham area gave much the same results as in the national survey. Dr. Alan Norton (1961) in a single hospital study concluded that there may well be a fall in the total patient population of one third over the next 20 years. In all three studies the critical factor influencing their conclusions was the shorter stay of patients in mental hospitals due allegedly to dramatically improved methods of treatment. What is also implied in these conclusions is that the present function of the mental hospitals will be largely taken over by community care in all its manifold guises.

So the parting knell of the British mental hospital was sounded, and what was tantamount to a memorial service to it was read by the late Dr. W. S. Maclay (1961), a former

[1] Panel discussion: other speakers included Michael B. Shimkin, M.D., R. Bruce Sloane, M.D., D.P.M., and William A. Steiger, M.D. Joint Meeting of the Section on Public Health, Preventive and Industrial Medicine, The College of Physicians of Philadelphia, and Pennsylvania Public Health Association, Region One, 25 May 1965.

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Principal Medical Officer to the Ministry of Health, in his Barton Pope Lecture given in Adelaide, Australia. Nor was the then Minister of Health, Mr. Enoch Powell, slow to join in the obsequies. In his Hospital Plan published in 1962 he announced that within ten years half the mental hospitals which he has described with more eloquence than accuracy as "majestic, brooding structures, dominated by the twin ideas of isolation and custodialism, housed in depressing and decaying buildings, suffering from acute staff shortages", would be pulled down and their function split between community agencies and general hospitals.

There can be no doubt that the Minister was influenced in framing his policy by the three papers I have mentioned and in particular that by Dr. Tooth and Miss Brook. I have a sneaking suspicion however, that the alacrity with which he seized on the suggested destruction of Britain's mental hospitals which, paradoxically enough, had excited world-wide admiration hitherto for their progressive approach and the development of the concept of the therapeutic community, was somehow influenced by political expediency as was the case with Willink Committee recommendations. So, to quote Miss Kathleen Jones (1963) "only in Britain has 'progress' taken the form of denying that the mental hospital has a useful function and planning for its abolition".

The publication of these papers and the Minister of Health's pronouncement split British Psychiatry in two. A state of civil—almost at times uncivil—war broke out between the protagonists and antagonists of 'The Plan'. At meetings of learned societies and in the correspondence columns of medical journals men spoke or wrote with fire in their bellies. Let it be said quite categorically that it was regarded as progressive to favour "The Plan" and grossly reactionary, if not sacrilegious, to oppose it.

I sided not with the angels. In so doing I felt rather like the small child in the fable of the Emperor's New Clothes who refused to acknowledge the existence of sartorial miracles which were not apparent to him. Similarly, I could not see the therapeutic miracles which were loudly proclaimed on all sides; nor could I see how mental hospitals with all their shortcomings had been transformed overnight from good objects into bad; nor could I see what progress had been made thus far in putting into effect the concept of "community care" which was first mooted as long ago as 1951 in the Mackintosh Report.

My opposition to The Plan was not a matter of sour grapes, for here in all fairness I must point out that my main hospital, Horton, was one of those earmarked for the attentions of the bulldozer.

I should explain that Horton served as a military cum civilian general hospital in the last War and did not function again as a psychiatric hospital until 1948. Starting then virtually from scratch the number of beds occupied rose rapidly to 1449 in 1958 about the time that there was the first appreciable drop in the number of resident mental patients in the U.K. as a whole, given in 1954 as 152,000. Furthermore, because there had not been time at Horton to build up an accumulation of chronic patients the opportunity to discharge them when the wind of change blew in their direction did not arise as was the case in many other hospitals.

It is also important to note that Horton although itself situated in Epsom, Surrey, draws all its patients from Metropolitan London. Its so called catchment area includes a deteriorating and socially disorganised sector of London.

In spite of, or because of, all these special circumstances my experience at Horton was so much at variance with alleged trends elsewhere that I decided to go to war myself and joined forces with the "reactionaries." As evidence of my belligerence may I quote from some of the broadsides I fired? For example in a letter to the Lancet (1963) I pointed out that Horton far from 'running down' was 'running up' at an alarming rate. The number of beds occupied had risen from 1449 in 1958 to 1503 in 1962. The annual number of admissions had soared from 1080 to 1753 in the same period. The increase had taken place in spite of a rise in the

number of out-patient consultations in clinics held in general hospitals in our catchment area from 4697 to 7370. The establishment of a Day Hospital in the Paddington area of London has no perceptible effect on the demand for beds in the parent hospital.

Again, prompted by Dr. Alan Norton's (1961) paper in which, if I may remind you, he had predicted a fall in the need for mental hospital beds, by one third in twenty years, I wrote again (Rollin 1961). In this letter I indicated what I considered to be the fallacies in his argument which was based on the improved response to modern methods of treatment, and the increased discharge rate from, or conversely the shorter stay in, hospital. Clinically his thesis was based, quite justifiably, on the largest, but the most unrewarding and perplexing of all psychiatric syndromes—Schizophrenia.

I challenged his therapeutic optimism and wrote, "It is my impression that the effect of modern methods is to precipitate a remission (in Schizophrenia) earlier than might otherwise have been expected. But what they seemingly do not do is to prevent relapses. How else can one explain the alarming number of relapses, represented by readmissions? So the patients come back, are further treated with perhaps less satisfactory result and go again. How often this cycle can be repeated depends on individual cases, but it can be frighteningly frequent. In effect, the 'open-door' policy of yesterday has been transmuted into the 'revolving-door' policy of today".

In the same letter, turning to the functions of the community in its care of the chronic schizophrenic, I said—

"Although ideally home is where the schizophrenic should be, all homes are not ideal. Schizophrenics tend to have strange, if not frankly psychotic, parents or relatives, and their influence may be actually detrimental to the welfare of the patients rather than the reverse. As a corollary of this, if one accepts, as I do wholeheartedly, and indeed as Dr. Norton does by implication that what he calls 'the changed atmosphere of the hospital' has subscribed to the patients' improvement then surely it may militate against their well-being if they are robbed of their props which the hospital affords, unless adequate substitutes at home or in the community are forthcoming.

And what of the schizophrenics who have no homes or no community to support them? In London in particular with its vast, shifting, multi-racial, multi-coloured, multi-lingual masses, it is by no means uncommon for discharged patients to belong nowhere. The problem of this rootless variety of chronic schizophrenic and, indeed, of others belonging to poorly integrated social groups, cannot be solved by sweeping it out of the mental hospitals under the social mat. Unless and until the community makes adequate provision for the ex-hospital chronic schizophrenics in their midst they will continue to erupt in a variety of ways. Some undoubtedly will find their way back to hospital—some, less fortunate perhaps, will swell the ranks of the unemployed and unemployable. Others will join the army of vagrants and elbow each other off the park benches, or lengthen the queues outside the flop-houses. Others still will embarrass the courts and prisons where their crimes, usually petty and purposeless, unless interpreted as a plea for care and protection, have landed them."

It was my belief that patients discharged from mental hospitals, not necessarily cured or even improved, were being redistributed in the community in a variety of socially retrogressive ways which led me to make a special study of male offenders admitted to mental hospitals.

If I may summarise my findings (Rollin 1963). In 1961, the first full year after the implementation of the Mental Health Act, 1959, 98 male offenders were admitted to Horton Hospital, a fivefold increase in the number admitted in 1959, *i.e.*, the year before the implementation of the new Act.

Seventy nine (81%) of those admitted were suffering from schizophrenia the characteristics of which were reflected in all facets of the enquiry.

In 63 (66%) offenders there was documentary evidence of previous mental illness. Forty-

one had had multiple admissions to mental hospitals and 47 had each spent an aggregate of more than six months in them. It was a fair assumption that a high proportion of the offenders were in fact chronic psychotics—that is, in all probability chronic schizophrenics, which must in some measure account for their social failure, evidence of which lay in the antisocial acts they had committed.

Fifty-three (84%) of those admitted had committed their offences within two years of the last recorded discharge from a mental hospital. Four (6%) had failed to survive even for as long as a day; 12 (20%) had collided with the law in under a month and within a year 43 (66%) had done so. In effect in a disturbingly high number of cases a hospital bed is in effect being exchanged for a prison cell. I concluded, "as for 'community care'—the currently popular psychiatric catchphrase—the question arises: *Does the community care?* The social failure of so many of the mentally ill offenders studied is in itself an index of the failure of the community to look after them. Seemingly, it is the case that the community, in London at least, is not over zealous in its efforts to look after the chronic psychotic in its midst".

The publication of this paper sparked off a recrudescence of the battle started in 1961 and I became the sort of standard bearer of the "reactionaries". The assault from the "progressives" was fast and furious, but one of those to rally to the flag was Dr. Anthony Flood (B.M.J., 1963) who elaborated part of my thesis. To quote from his letter—"For the past two years I have been seeing the same problem from another aspect.

"Of the 200 men whom I have interviewed in a hostel for vagrants (in the Bristol area) 50 had previously been in mental hospitals and of these 26 had been diagnosed as suffering from a schizophrenic illness. In the latter group 18 had been in prison, mostly on more than one occasion. There is, for many chronic schizophrenics in the present day, a trilogy of mental hospital, flop-house, prison, and in that order."

It might be argued, indeed it has been argued, that my views are unduly jaundiced and prejudiced and are based on one hospital drawing its patients and its experience from London and is therefore the expression of a "metropolitan phenomenon." Even if this were true, the Metropolis with a population of ten million cannot be ignored and what is true for London is probably true for other large conurbations such as Birmingham, Liverpool, Glasgow, Leeds, etc. Indeed, workers in the Leeds area 200 miles from London (Gore *et al.* 1964) claim that far from a reduction according to the Hospital Plan in mental hospital beds to 5840 by 1975 it is estimated that the bed needs will probably be 9,000–10,000 in their area. They conclude with the same pessimistic note as I have sounded.

"Patients can be discharged and beds can be emptied, by administrative decision, but, in the absence of some substantial and favourable change in the situation, this can be achieved only at the cost of much hardship to patients and their families."

I am aware that I have gone thus far without defining what I mean by the slogan "community care." Perhaps my omission is based on the fact that in all honesty I am not at all sure what it in fact does mean. As I see it "community care" means any method used by individuals or by medical or social agencies aimed at the care of the mental sick outside the mental hospital. It would be as well, then, to examine what facilities exist, in fact rather than in fantasy, in Britain at this point in time.

If I am correct in my notion of what community care means then the following must play their part.

Psychiatric Units in General Hospitals

According to Mr. Kenneth Robinson, the present Minister of Health (Hansard, March 1965) there are 5,000 beds available in general hospitals for the treatment of psychiatric patients in the whole of the U.K. Praiseworthy as these units may be in principle the number of beds so far available is ludicrously small. Because they are scarce these units are available only for the treatment of new acute cases. If after discharge they relapse—and most psychiatric

illnesses have the distressing habit of so doing —they are passed back to the mental hospital who must cope with their readmission from the 2nd to the Nth time.

Never having worked in such a unit I cannot speak with any authority, but it is self-evident that it has grave deficiencies. It cannot have, for example, anything approaching the occupational, or recreational facilities of a large well-established mental hospital. And without these facilities there can be no morale, no feeling of community with others, and without this so much therapeutic endeavour is blunted.

Day Hospitals

Farndale, a leading British authority on Day Hospitals, writing in 1963 describes three types, the most important of which numerically is the psychiatric day hospital where patients (many of whom would otherwise have been in-patients) attend daily for treatment. Of these there were 45 individual day hospitals in the U.K. with a maximum of about 2,000 places daily.

There is certainly a place for these hospitals, but the total accommodation even for those eminently suitable for such treatment, is pathetically inadequate. Even so they are extravagant in accommodation and staff relative to the numbers of patients treated; and the greatest possible care must be taken to ensure that these patients are adequately supported after hours: their psychoses do not 'close down' at week-ends or between 5 p.m. and 9 a.m.—even if the hospitals do.

Hostels

In any community care program no matter how constructed residential hostels in large numbers will have to be provided to take in the untold thousands who will be theoretically discharged from mental hospitals. Historically speaking, a token effort in this direction has gone on for many years as witness the hostels provided by the Mental After Care Association, a charitable organisation. This association deals splendidly with a tiny percentage of the problem of the ex-mental hospital patient in the same way as the Royal Hospital, Chelsea, deals splendidly with the problem of a handful of army pensioners. Again, where the interests of a community are directed towards a community interest tangible results are obtained. For instance, the most satisfactory hostels I know are the two supported by the Jewish Welfare Board in London which between them accommodate about 50 patients. Even so the patients must be highly selected and the cost of running the hostels is extremely high, far higher indeed than would be tolerated by a public authority.

But for the hostels actually functioning in the community and supported by the local tax payers the number of mentally disordered people accommodated—and I again quote the Minister of Health (Hansard, March 1965) as my authority—was 1,523 at the end of 1963. Nor have these miserably few people been accommodated without strong opposition from the local community. Once the establishment of such a hostel is mooted there is an immediate outcry from the local inhabitants. The principle reason for their protest is that such a hostel established in their midst will lower the value of their property (and to tell the truth, it does!), but I know full well having given evidence at a public enquiry that the major reason is fear—fear for their own safety and that of their kith and kin. Even in this day and age it would be highly irresponsible to exaggerate the extent to which mental illness is both understood or tolerated by the community at large.

Out-Patient Clinics

It has become the order of the day that mental hospitals in the U.K. staff psychiatric out-patient clincs in general hospitals in the catchment areas which they serve. Horton Hospital, for example, now runs such clinics in three separate hospitals, a total of five sessions a week. They illustrate, in fact, Parkinson's Law: the more the facilities provided the more people emerge to avail themselves of them. The number of patients handled annually by a

very limited staff of psychiatrists had reached by 1964, 1368 new and 6132 old. The sheer weight of numbers alone precludes prolonged psychotherapy except for a tiny minority. For the rest the clinics are for the most part sorting houses, or, frankly, pill-peddling sessions.

Ancillary Staffs

By these I mean trained workers in the field of mental health other than medical practitioners and nurses, although in respect of both these it should be mentioned that the numbers employed are at danger level. If community care is to function at all then it is absolutely essential that there is a plentiful supply of such key personnel as psychiatric social workers, social workers, mental welfare officers and the like, who can act in society as the antennae of the psychiatrist. But where are they? Examine for a moment the present situation with regard to the most important of these ancillaries the P.S.W. In a devastatingly frank assessment of the psychiatric scene in the U.K. Richard Titmus (1963) writes "In 1951 eight psychiatric social workers were employed full-time by the 145 local health authorities. In 1959 there were 26; an increase of 2.25 per year. At this rate it will take another 53 years (A.D. 2014) before someone can say that there is an average of one psychiatric social worker to each authority". I cannot resist quoting the final sentence from the same author's chapter because it is so much in concert with my own views and those of other "reactionaries". Professor Titmus says, "At present, we are drifting into a situation in which, by shifting the emphasis from the institution to the community—a trend which, in principle and with qualification, we all applaud—we are transferring the care of the mentally ill from trained staff to untrained staff or ill-equipped staff or no staff at all".

The Family

It seems to me patently obvious that if community care means anything at all then those most vitally concerned with it must be the families of the patients themselves. But this is not a new divine revelation. Plato in his Republic called upon the relatives of the insane to watch over them at home and went so far as to suggest penalising those relatives who failed in their obligations and permitted them to wander abroad.

Furthermore, it must be remembered that even before mental hospitals became almost by definition evil institutions there were far more psychotics in the community than in the hospitals. Very often, indeed, it was only when the key support in the family collapsed, usually when the guilt-ridden mother died, that the unfortunate psychotic had to be admitted: the other members of the family were usually less dedicated to the cause. What is equally to be remembered is that even before the Mental Health Act 1959, with all its good intentions, came into operation it was most difficult to keep a patient in hospital in the face of a determined effort on the part of his next-of-kin to get him out.

Now that the family is not only encouraged, but enjoined, to have their psychotic brethren at home a good deal of most revealing research is going on into their social effects on the family and on the community. Some of the results are discouraging. Dr. Peter Sainsbury and Dr. Jaqueline Grad (1962) wrote: "Our tentative conclusions from a preliminary analysis of the problems that these 60 patients were causing their family at the time of referral (to the Psychiatric service) were that in 36% of the families social activities had been restricted; in 25% the job of a family member had been affected; and that 40% of the cases presented some problems of management (in 20% this was severe). The health of the informant was affected psychologically in 32% and physically in 36%; the health of other family members was affected in 44% of households. Family income was diminished on account of the patient's illness in 33% of the households (severely in 20%) at the time of referral. These figures were higher in the families of those patients whom it was decided to admit."

These sober findings indicate all too clearly

that the price the family has to pay for keeping its mentally ill member at home may be heavy indeed.

The work of these two authors is of vital importance because it emanates from Graylingwell Hospital, Chichester, where the former Physician Superintendent, Dr. Joshua Carse was responsible for the "Worthing Experiment". It was this much publicised experiment in home-centred psychiatry that blazed the trail for community care elsewhere in England and abroad.

The obverse of the effect of the patient on the family is the effect of the family on the patient. There can be no doubt that, as I remarked earlier, some families are anything but ideal physically or emotionally to cope with the mentally ill. I was intrigued by the phrase "a one-man chronic ward" (Freeman and Simmons) which describes precisely the atmosphere that pervades some homes. What is more, I have seen patients returned to hospital from their homes pathetically deteriorated from sheer neglect.

The General Practitioner

The last major role in this vast undertaking is that which should be played by the general practitioner. For reasons I have outlined, doctors in Britain are a scarce commodity. Those in general practice are already overworked and not a little dissatisfied with their lot. It would be surprising if they took kindly to the additional burden which the psychiatric millennium must impose on them. Even if this were not so it is doubtful if, with all the will in the world, the majority of these doctors are adequately trained psychiatrically to fulfill their additional role.

I have attempted to describe as best I can the field of community care as it exists in Britain today. The field is, you will appreciate, green and lush only in isolated patches. Some of it is paved with good intentions: but for the most part it is an arid waste which for lack of money and personnel cannot be cultivated, now or in the foreseeable future.

I have also tried to describe the forces deployed over virtually the same field that are engaged in the battle for the destruction or preservation (and improvement) of the mental hospitals, that is, the battle between the "progressives" and the "reactionaries". On the side of the "progressives" are the statisticians and politicians, both vociferous, wily campaigners who, you will remember, won an epic victory over the forces of common sense in the Willink war of 1957. But the 'reactionaries' also have an ally unfortunately far less wily and too soft spoken—the historians.

These academic gentlemen will counsel you to study psychiatric history, and for the purpose of this campaign it is necessary to go back not as far as Plato but only three or four decades. This brief period in the history of psychiatry is littered with the skeletons of false gods who have left the imprint of their feet of clay on its all too easily forgotten pages. They will remind you of a variety of dramatic procedures all promising to revolutionise the treatment of mental illness, and as a consequence, empty the mental hospitals. As examples they will cite Insulin Therapy, Electro Convulsive Therapy and Pre Frontal Leucotomy, and might add with an attempt at wit that never was a Nobel prize more ignobly won. They will go on to remark that the contribution of the tranquilisers has yet to be evaluated and that there is growing evidence that even their palliative effects may be costly in terms of permanent damage to the Central Nervous System. They may even become a little stern and wag a reprimanding finger whilst emphasising that each and every procedure named bears the scientists' mark of Cain—Empiricism!

Finally, they will point to the undeniable fact that with our non-existent methods of prophylaxis and a worldwide population avalanche, the sheer volume of mental illhealth must increase. Furthermore, they will conclude, with what dramatic emphasis they can muster, that if the mental hospitals are destroyed and community care succeeds in being

no more than a resounding catchphrase, then social chaos will result. And the psychiatric clock will go back a hundred years.

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Behavioral Reactions to Surgical Procedures[1]

By FLOYD S. CORNELISON, JR., M.D.[2]

THE form of human illness always deserves close scrutiny. A patient's disorder may be structural, physiological or psychological, and in each of these there may or may not be an awareness of pain, discomfort or unusual affect. However, in the interest of effective evaluation and treatment, the physician can benefit from an appraisal of these different types of disorders, their manifestations and the temporal relationship which one may have to another.

In this paper I would like to consider the behavioral reactions to surgical procedures as one type of illness complex which the patient may present. At the outset, let me say that of all physicians who observe the response of patients to operative surgery, it is the surgeon—not the psychiatrist—who is the more experienced. This is particularly true of the normally healthy adaptive reactions to surgery. It is the unusual or abnormal response to a surgical procedure which may bring into action the psychiatrist, who then observes and attempts to understand the patient who has reacted toward a structural change in his body in what may be considered an unhealthy manner.

There are four phases in the experiencing of a surgical procedure. These are the anticipation phase, the procedural phase, the recovery phase, and the assimilation phase. For certain types of traumatic or accidental events in the life of a patient, the anticipation phase may be brief or entirely lacking. For example, in emergency surgery following an automobile accident, the patient may not regain consciousness until after he has undergone the operation.

[1] Read before the Section on General Medicine, The College of Physicians of Philadelphia, 22 March 1965.

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The Anticipation Phase

If a patient has been told of the need of an operative procedure, and he has some period of time to think of this matter before reaching the operating table, there may be a modification of his usual psychological state, usually for defensive purposes, as the result of anticipating the operation. The personality of the individual as well as the life situation which precedes an anticipated operation are determining factors in the final behavioral reaction to surgery. Threats of the surgical danger, the amount of pain to be expected, the hope of a cure from surgery, as well as the patient's attitude toward the diseased organ or the body part, are of particular importance. The modification or excision of a portion of the patient's body to which he is emotionally attached may be experienced as a significant loss.

The excessive anxiety and fear resulting from anticipating an operative procedure can be interpreted as a threat of castration (1), meaning the loss of the primary sexual apparatus. Since this type of human feeling, sometimes not clearly represented in consciousness, is based largely upon the development of a fear of the loss of body organs at an early age, the adult's attitude toward an anticipated operation is considered to be, in large part, determined by experiences in infancy and childhood. Operations early in life accentuate fear in the child of a loss of his body parts. Anticipating an operation also means for the patient at any age the mobilization of large amounts of aggression which usually find some means of expression, in one way or another eventually, and this itself can enhance the degree of anxiety and fear.

Psychological reactions to the surgeon, especially in cases where patients know and have a meaningful relationship with their physician, may be expected, since the patient's atti-

tude toward having part of his body removed may depend, to a great extent, on his feeling about the person responsible for removing the body part. In many instances physicians take the place of parental figures for patients, even though there may be no conscious awareness that this is occurring. Dependency relationships or overt hostility toward the surgeon may occur. This may not be due to the specific personality or functions of the surgeon, but may be due to the previous life experiences of the patient.

It has been observed that patients displaying a moderate amount of anticipatory fear *before* being exposed to planned physical stress or pain seem to be less likely to develop emotional disturbances at the *actual time* of the physical stress or pain (2). On the other hand, individuals who display a very high degree or very low degree of anticipatory fear *preceding* an actual physical stress stimulus, may have considerable emotional difficulty at the *actual time* of the physical stress.

The patient who does not react appropriately to the occasion of surgery may be investing in the surgical event many of the psychological conflicts which have evolved from previous life experiences. The anticipated dangers of surgery may be largely irrational, but the patient cannot dispel them. Repressed inner dangers may be touched off by an external threat, and this may prevent the patient from gaining any effective reassurance from actual knowledge about the value of the surgical procedures to be performed. This also may account for the person's inability later to correct or modify his excessive anxiety.

Surgical procedures are more likely to evoke greater degress of fear if the patient knows that the pain, the permanent damage or possibility of death is relatively high.

The Procedural and Recovery Phases

Normally only the surgeon and the anesthetist have sufficient information regarding the reaction to the surgical procedure itself to make judgment about the response, if the patient is not conscious during the operation. In some instances there seems to be a great deal of excessive movement during operative procedures, but this may be a function of the depth of anesthesia state and not a behavioral response to the knife.

During recovery, a number of reactions may be observed following surgery. Except for the overt psychotic states, often complicated by toxic drug reactions, this often is a quiet period for the individual undergoing surgery. What is he thinking? How does he reflect upon the immediate past experience? Drawing from many hours of bedside interviews following surgery and the visits to my office by patients who, in psychiatric treatment, speak occasionally of their memories of surgery and their reactions following the operation, as well as taking a few pages from my own personal experiences with surgical procedures, here are some of the common thoughts and feelings: "Will I live? Did they do anything in addition to what the surgeon said he would do? Was the operation successful? Will they have to do any more cutting?" The patient, in effect, wishes to learn if he is still intact.

Regarding interpersonal relationships, broken during the operative period, the patient recovering from a surgical procedure often wishes to know the whereabouts of the important persons in his life, he wants to know if they realize how things are, and he expresses some wish to make a gesture of communication toward them. He wants other people to know about him.

An outline of some of the basic principles in understanding human reactions to surgery is the following:

a. Ego identification—A realistic awareness of one's body, the self, the "I", and the boundaries and the nature of the existence of the person.
b. Object relations—A realistic appraisal of interpersonal relationships, contacts with other people and outside things in a world of time, space, mass and energy.
c. Progression toward human maturity—A continuation of the process of carrying out appropriate integrated biological

functions at a given age, in given circumstances.

Each of these, following surgery, can be considered as important determining elements in the normal or in the abnormal, unsatisfactory, uneconomical, and pathological reaction to an operation.

After surgery, excessive anxiety may suggest an inability to accept the realism of the self. A severance with the realistic other-than-self world, as in psychotic states, indicates gross withdrawal from outside objects, including persons. An interruption of normal progression toward intended functions may be either primary or the secondary result of either impaired ego identification or diminished object relationships.

Two illustrative cases, condensed drastically for purposes of this presentation, are:

A 40 year old man became anxious to the point of panic, immediately following removal of one eye, due to malignancy. The sudden threat of partial blindness and possible death could not be accepted by him. His behavioral escape, to avoid the inconsistency between his own image and the real imperfect self, resulted in a suicidal attempt. Later, acceptance of his own body, and his capacity to continue appropriate functions during life, were gradual, and he returned to a more normal pattern of behavior within a few weeks.

A 35 year old unmarried nurse began to hallucinate (she saw babies on the window-sill) following hysterectomy for suspected neoplasm. Prior to the operation she had not been informed adequately that her uterus might be removed. The image of her body and dreams of fulfillment of feminine functions were ruptured instantly when she learned the truth in the recovery room. A period of time, the reestablishment of her body-concept and of personal relationships resulted in recovery from the acute behavioral symptoms which had followed the operation.

The Assimilation Phase

This period of accommodating to surgical procedures is merely an extension of the recovery phase. The same factors which I have outlined above are active, as well as the important element, time. Since life is not static, the adjustment to the final effects of surgery depends upon life circumstances as well as the individual's background, personality and his capacity to respond.

In reviewing some of the literature regarding *reactions to surgery*, I was impressed with one point about which I would like to comment here, in concluding this presentation. The human reaction to a threat of loss of body part or death, felt as due to a surgical procedure, is emphasized repeatedly by many different authors. However, the hope of recovery of important functions, or a new lease on life *due* to surgery, is not stressed in the literature. Perhaps this single point should be underscored here: Surgery, actually more frequently than may be realized, may provide patients a greater degree of security than threat to human existence. This may account for the fact that long-term serious mental illness is seldom precipitated by surgical procedures. Even violent psychotic reactions usually are transient.

Certainly, for the common variety of man, surgery offers no serious threat. Titchener (3) puts it this way: "Even the . . . 'neurosis-finder', who can see psychopathology everywhere, must admit that there are some individuals who seem to have no personality troubles when they become seriously ill. There are some patients, who are well enough integrated, finished, mature adults, who can withstand the real and imagined threats of illness and prospective treatment . . ."

Since many of us, including children, need surgery from time to time, we should learn more about the nature of the threat of surgery, in order to provide help for those who find this experience a difficult problem.

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John Hunter (1728-1793): Creative Surgeon[1]

By BERNARD L. SEGAL, M.D.[2]

THE career of John Hunter is one of the most amazing in medical history. Although hampered by lack of formal education and little awareness of the work of surgical colleagures at home and abroad, yet by force of industry and an irrepressible curiosity, he became the foremost surgical investigator of his age, a leading surgeon in a world metropolis, and the founder of the greatest tradition in the annals of surgery. He towers above his contemporaries, his predecessors and many of his successors. As Ambroise Paré is the greatest figure in the history of French surgery, so John Hunter is, by common agreement, the greatest in the history of British surgery.

John Hunter was born in 1728 at Long Calderwood, Lanarkshire, Scotland, the youngest of ten children. His father, who was nearly 70 years of age at the time of his birth, died when John was only 10. The son was an awkward youth, a poor student who left grammar school ignorant of the learning it was supposed to impart. Natural history, which would have captured John's interest, unfortunately then held no place in the curriculum. He skipped his classes as often as he dared and when he attended, it was often in body only. His exasperated teachers finally wrote him off as an idle dullard, irredeemable by punishment or reward. Taken out of school at the age of 13, terminating the only formal education he would get, he could barely write English and had acquired a permanent distaste for the halls of academe.

Tiring after several years of farm life, he wrote to his elder brother William, who had become a celebrated teacher of anatomy, expressing a desire to assist him in his dissections. Receiving an invitation from his brother to come to London, John arrived there in 1748, aged 21 years. He immediately began to dissect under the eyes of his brother and for eleven successive winters his life was passed in the dissecting room. William Hunter had become a giant of London medicine, having studied with the eminent obstetrician William Smellie. William had won favor with James Douglas who got him into St. George's Hospital as a surgical student, a privilege not granted to every Scottish aspirant. After qualifying, William developed a thriving practice and leased a house in the great piazza of Covent Garden. This home was large enough to accommodate his anatomy classes, having a dissecting room and consulting offices.

John arrived in London early in September, 1748, after traveling on horseback over the same route that Roderick Random took, across the Tyne River and following the great northern route southwest to London—a two-week journey. It must have been an embarrassing moment for the brothers at their first meeting after a separation of eight years. William displayed the air of a rich and fashionable Londoner, with a pigtail peruke and a professional tone of aloofness. He was strikingly handsome, with a delicate profile, long slender hands, and a graceful manner. John was raw; no wig covered his coarse red hair, no conversational niceties softened the harshness of his voice. Rugged and boistrous, he reeked of stable and fields; and his natural pugnacity was intensified by the anti-Scottish sentiments around him. William, though dismayed by John's uncouthness, welcomed him as an assistant in the anatomy course. John often visited the lively places on Covent Garden, including coffee houses and taverns, patronized

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FIG. 1. Bust of John Hunter above the entrance to St. George's Hospital, London. Photograph courtesy of Dr. Fred B. Rogers.

by intellectuals, gamblers and prostitutes. Night or day, Covent Garden was never silent. Quacks hawked their nostrums for cancer and the "French-pox". Jugglers, Punch and Judy shows, street peddlers—all were constantly crying out their wares.

When William Hunter taught anatomy, body snatching was in vogue. He had to procure scores of bodies within a nine-month period and so delegated his rough-and-ready brother to handle the negotiations with the resurrectionists. John gave the 'ressurectionists' drinks and accepted drinks in return. Almost certainly he snatched bodies himself. The body-snatchers liked dealing with John and they gave him preferential service in human cadavers.

John Hunter attended the surgical lectures of William Cheselden, who at the age of 61 had few peers as a teacher. When John returned to Covent Garden for the fall term, he showed such proficiency at dissection that William made him instructor in his School of Anatomy. William also arranged for John to study under Percival Pott who, at age 38, succeeded Cheselden as the leading figure in British surgery. From Pott, John learned the value of simplicity, not only in surgery, but in medication and bandaging. In 1755, he entered Oxford University but remained there less than two months. "They tried to make an old woman of me", he said sometime later. "They wanted to stuff me with Greek and Latin at the University, but these schemes I cracked like so many vermin as they came before me."

John Hunter was soon admitted to a partnership in Dr. William Hunter's lectures, but here his defective education and his inability to express himself clearly were sources of embarrassment. Despite his lack of success in the lecture room, he continued to be of great assistance to his elder brother and began to make important anatomical discoveries. He demonstrated the single continuous passage from the testicles to the vas deferens. The Hunters worked together on the lymphatic system and the afferent blood flow to the heart. They also prepared a treatise on congenital herniae. William, in 1774, completed his Master-work, *The Anatomy of the Human Gravid Uterus*. Published in elephant folio by the famed Baskerville Press of Birmingham, it remains one of the most impressive books of all time.

In the summer of 1754, John Hunter was admitted as a surgeon's pupil to the hospital with which his name would be forever associated. St. George's Hospital had been founded

in 1733, the founders of the hospital having broken away from the Westminister Hospital Board. It was constructed at Hyde Park Corner, in the parish of St. George. Twenty-one years after its founding, John Hunter traveled the mile and a half to St. George's Hospital from his quarters in Covent Garden. The hospital was then almost four times its original size. With its 250 beds, each costing 30 pounds a year to maintain, St. George's was then the largest of London's voluntary hospitals. The general wards where John received most of his tutorage in postoperative methods held about 15 beds each. (There is a vivid account of the poor general conditions and nursing care in John Kobler's book, "The Reluctant Surgeon." A nurse then received a salary of six pounds a year and worked under the most horrible conditions.)

John was belatedly persuaded to enter Oxford, but his cultural deficiencies were the despair of men who valued him most. He found it hard to express himself; many of his ideas were garbled or lost to posterity altogether. In 1760, he joined the army as a staff surgeon and for three years was deep in the practice of military surgery. During the Seven Years' War, in 1761, he accompanied the British expedition to Belle Isle. During that seige he found ample opportunity to treat gunshot wounds, a skill for which he was later to gain renown. While he was less engaged, he found time to conduct investigations in experimental physiology. He studied the digestion in lizards and snakes during hibernation and, among other things, the process of hearing in fish. He also served in Portugal for four years as a military surgeon.

By 1763, the War was terminated and John returned to London. In order to increase his income, he decided to teach anatomy in private classes. During his spare time he continued making anatomic and physiologic investigations. To obtain specimens for this research, he obtained the bodies of animals that had died in the zoos of London and elsewhere and purchased rare animals, often spending money he could ill afford. In 1767, Hunter was elected a Fellow of the Royal Society. His election probably was the result of recognition of his devout interest in comparative physiology. He was later appointed a surgeon at St. George's Hospital, in 1768; among the most renowned of his students there were Astley Cooper and John Abernethy.

John Hunter longed to open an anatomical school of his own. In order to obtain financial security, he allied himself with a family of Scottish barbers and toothdrawers, the Spences. His success in practice came slowly and he accordingly wrote a treatise, *The Natural History of the Human Teeth*, published in 1771. His school of anatomy was located in Golden Square. On July 22, 1771, he married Ann Home, described as a lady tall and slender, with a heart-shaped face framed by golden curls, deep blue eyes and a full generous mouth. She was a harpsichordist, composer and painter, and fitted effortlessly into London's coterie of blue stockings. They made an incongrous pair; John, plain as salt, fourteen years older, heavy-set and disheveled, preoccupied with the problems of dissecting room and sick ward, and Ann, young, cultured and sophisticated.

William, at this time, was hoping for the support of the Chancellor of the Exchequer, George Grenville, in an ambitious undertaking. He had requested a grant of land on which he would erect a museum of anatomy and a surgical school; he proposed to invest 7,000 pounds of his own capital to endow a perpetual professorship. Granville never replied to this proposal. William became furious and bought a three-story mansion in Great Windmill Street in Soho. He enlarged it to contain an amphitheatre, dissection and lecture rooms and hall for his collections. He lived there during the rest of his life. The Great Windmill Street School, as it was properly called, opened in the fall of 1767. It was an immediate success, attracting not only a large medical following, but intellectuals such as Edmund Burke, Samuel Johnson, Joshua Reynolds and Thomas Gainsborough.

In 1767, John sat in his Golden Square dispensary, fingering a lancet he had dipped

into pus excreted from venereal sores. He inoculated himself to study the natural course of this disease, and developed the familiar primary lesion of syphilis, since known as the Hunterian chancre. Throughout the remainder of his life he suffered from numerous chest and joint pains, probably due to secondary and tertiary syphilis.

In 1772, he capably described the digestive action of the gastric juices. In the same year, he was appointed to the staff of St. George's Hospital and shouldered a heavy burden of teaching. John Hunter became a truly creative surgeon. He discoursed on the subjects of inflammation, healing and repair, and in time found himself teaching students from many lands. Of his foreign pupils, there were Gimbernat, Sömmering, and Wolstein. Edward Jenner, an English country doctor, journeyed to London in 1770 to attend John's lectures. He pondered using a cowpox vaccine to prevent smallpox, and was goaded to try the experiment on humans by John, with the statement, "Don't think, try it." On May 14, 1796, Jenner made two incisions into James Phipp's arm and inserted lymph from a cowpox lesion on the hand of a milkmaid, Sarah Nelmes. As Thomas Jefferson later wrote to Jenner, "You erased from the calendar of human afflictions, one of its greatest. Yours is the comfortable reflection that mankind can never forget that you have lived. Future nations will know by history only that the loathsome smallpox has existed and by you has been extirpated." The belt given him by an Indian chief of Canada remained Jenner's proud possession, together with the hide of the calf that infected Sarah Nelmes, and John Hunter's letters to him. The hide of the cow is now in the St. George's Hospital library. Among American pupils visiting John Hunter were William Shippen, Jr., and John Morgan, from Philadelphia, Benjamin Waterhouse from Cambridge, Mass., and Richard Bayley and Wright Post from New York City. Philip Syng Physick, of Philadelphia, another pupil, who introduced Hunterian philosophy into American surgery, was acclaimed by his contemporaries as the "father of American surgery." It was fitting that the American Philosophical Society, in 1787, at the urging of its president, Benjamin Franklin, elected John Hunter an honorary member.

In 1772, Hunter was seized by severe chest pain, became ashen gray, but survived the attack. Jenner visited him at Bath and surmised that he was suffering from angina pectoris. John came to despise and feel ashamed of his body for its failings.

In 1783, the lease on his brother's house at 24 Jermyn Street expired and John moved into Leicester Square. This property was heavily mortgaged and his investments were rather reckless. He took time then, however, despite his large clinical practice, to work on his many animals and to establish the museum.

In 1783, Hunter procured, at a cost of 500 pounds, the "kidnapped" body of a famous Irish giant, Byrne O'Brien. He disarticulated the skeleton and it occupied a prominent place in his museum of natural history. In the same year, the Royal Society conferred its Copley Medal upon him in recognition of his important discoveries in natural history. At Earl's Court he experimented with plants, attempting to answer why they grew upward. He obtained enough pearls to string a necklace by artificially stimulating Scottish river mussels. He was interested in the growth of bones, ovarian productivity, and the physiology of the pregnant uterus. Brotherly relations turned sour over a squabble about pathologic specimens and reached an ugly climax in 1780, when John claimed discovery for the structure of the placenta—which had actually been described by William in 1755. William died in 1783: his alienated brother did not attend the funeral.

In 1785, John's anginal episodes became recurrent. In that year he devised a famous operation for the cure of arterial aneurysm. This consisted of tying an artery by a single ligature at a distance high in the healthy tissues. A year later, he published his work on venereal disease. He mistakenly believed that syphilis and gonorrhea were identical because he had developed the symptoms of both diseases through a single inoculation. This errone-

ous conception was later corrected by Philippe Ricord of Paris. In 1792, John Hunter studied human artificial insemination.

John Hunter had his portrait painted by the famous Sir Joshua Reynolds. He proved a difficult subject and the finished portrait did not please the artist. John consented to pose again. On the table by his elbow, he reproduced two folio volumes labelled, *Natural History of Vegetables* and *Natural History of Fossils*. In 1792, John's health was failing and William Clift, a new apprentice, aged 17, appeared at 28 Leicester Square. Clift proved equal to whatever tasks John assigned him, whether secretarial duties, dissection or injections of specimens. Clift selected and remounted the exhibits worth keeping. He loved his master to the end of his days.

In 1792, Hunter transferred his surgical lectures to his brother-in-law, Everard Home, and devoted much of his time to the completion of his famous work, *Treatise on the Blood, Inflammation and Gunshot Wounds*. This was not published until 1794, the year following his death. Hunter had said that his "life was in the hands of any rascal who chose to annoy and tease" him. There could be no doubt that the violent disagreements he had with his colleagues at St. George's Hospital hastened his death. This occurred on October 16, 1793, following a meeting of the Board of Governors, at which a colleague had directed some disparaging remarks at him. The bitterest wrangle at the hospital centered around the training of the hospital students. In John's view, the surgeons skimped their obligations. To shame his colleagues, he delivered additional lectures at home to his pupils; arguments with his colleagues increased in fervor and financial worries on top of overwork and the harrassment of his rivals strained John's heart to the limit. It shook Clift to see him day after day supine on a sofa bed, clutching his chest and gasping for breath. During his last Board meeting, before his death, after being insulted by a member of the Board, his chest pain became more severe. He stopped speaking, struggled to control his temper, staggered into the adjoining room, groaned and fell senseless. He died during the afternoon, without regaining consciousness.

The autopsy report showed that John Hunter had severe arteriosclerosis of the aorta with an incipient aneurysm. The internal membranes had lost their natural polish and were studded with opaque white spots, raised higher than the general surface (a picture consistent with the terminal ravages of syphilis). John went to his grave with scant ceremony and no official honors. He was buried in the crypt of St. Martin-in-the-Fields Church where the Hunters had worshipped for many years. In three carriages following the hearse, there followed Ann, their young children John and Agnes, Matthew Baillie, Everard Home and a few friends.

In 1859, at the insistance of Frank Buckland, the body was reinterred in Westminster Abbey between the graves of David Wilkie and Ben Johnson. A brass tablet erected by the Royal College of Surgeons of England now marks the original site of burial in St. Martin's Church.

John Hunter was remarkable both for his achievements and his personality. One who reads about his career is filled with admiration for his genius, is entertained by his shrewd and witty remarks, and is impressed by his avid pursuit of knowledge.

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Dr. Paul-Ferdinand Gachet: Vincent Van Gogh's Last Physician*

By REMO FABBRI, JR., M.D.†

A PAINTING by the Dutch artist, Vincent Van Gogh, is the best introduction to the curious figure of Dr. Paul-Ferdinand Gachet. Van Gogh's brightly colored portrait of this French physician[1] presents a pensive figure, leaning on a table, his head in his hand. The painting indeed affords a striking visual experience; but it also brings several questions to mind. First, why had this man been painted by one of the outstanding artists of the nineteenth century? Was Gachet merely a village doctor who had agreed to pose for a mendicant artist? Or, was there, instead, some profound relationship between these two men that had led Van Gogh to reveal a deep understanding of the doctor?

Investigation of this problem revealed that Gachet had actually been the last physician to care for the troubled Vincent Van Gogh. After the artist's severe breakdown and hospitalization in the south of France, Vincent returned to the north where his brother, Theo, had arranged for him to live in the village of Auvers-sur-Oise under the care of Dr. Gachet. The choice of this physician was not a random one, for Dr. Gachet was eminently suited for the care of a patient such as Vincent Van Gogh. First, in an era when few doctors were knowledgeable in the care of the mentally ill, Gachet had studied the subject and, although a general practitioner, had actually treated mentally disturbed patients. Second, the physician was an artist himself and had long associated with artists, treating many of them for various medical and emotional problems.

Gachet's background and education are both interesting and relevant. He was born in 1828 in Lille, Flanders, the son of a well-to-do French family and while a student lived both in this northern city and in several nearby Belgian cities. It was during his years among the Belgian Flamands that Paul developed a keen interest in the fine arts. He began to paint and signed his canvasses with the Flemish name "Van Ryssel," meaning simply "from Lille," his own birthplace. Curiously, he continued to use this throughout his lifetime and consciously identified the artistic side of his personality with his early ties to the north. In 1848, young Gachet journeyed to Paris to enroll at the Faculty of Medicine. His university career is interesting from two standpoints, both pertinent to the present discussion. First, he lived among the students of the *Ecole des Beaux-Arts* and continued to develop his own abilities as an artist. Second, Gachet quickly found that two aspects of medicine fascinated him most; the new work being done in the field of mental illness, and the new and controversial approach in medical therapy known as homeopathy. Because the French medical students had a great deal of freedom in the determination of their curricula, Paul overloaded himself with externships at the famous Parisian mental hospitals, the Bicêtre and the Salpêtrière where he worked in the

This paper is a condensation of various parts of the author's doctoral thesis, *An Inquiry into the Life and Thought of Dr. Paul-Ferdinand Gachet*, which was accepted by the Yale University School of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine. The study was in part made possible by the receipt of a Logan Clendening Travelling Fellowship in the History of Medicine.

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[1] This portrait is now housed with the rest of the Gachet collection in the Jeu de Paume Museum, Paris.

service of Professor Falret, himself a student of the great psychiatric reformer, Philippe Pinel.[2]

When Gachet began to study psychiatry during the middle of the nineteenth century, men were still working to improve upon the therapeutic regimen known as the moral treatment of the insane. These humane principles had first been advanced at the end of the eighteenth century by men such as the Tukes in England, Chiarugi in Italy, and Pinel in France. Gachet was fascinated by the problems of fear and prejudice that had faced the reformers and incorporated into his own self much of their courage and zeal. In addition, he was also influenced by the writings of Hahnemann who, in effect, was one of the first men to attempt to build a logical and coherent system of medicine out of the chaos of eighteenth century medical therapy. Gachet was also impressed that Hahnemann too advocated a rational and humane treatment of the mentally ill and had himself attempted to work with the mentally distraught.

In addition to his interest in what had been written about mental illness, Gachet was also fascinated by the mental patients themselves. His own enthusiasm was contagious, and he fascinated his artist friends with tales of the Salpêtrière. Curiously, he even secured permission from Professor Falret to sketch the distraught patients in what seemed their most characteristic positions.

When Theo Van Gogh first met Dr. Gachet in 1890, he was impressed by this general practitioner's background in psychiatry. We may gain some insight into Gachet's ideas through his own writings on the subject. His first essay was his doctoral dissertation on the problem of Melancholia, written after he had transferred to the Medical Faculty of Montpellier in the south of France. The paper itself is a compendium of the principles of the moral treatment of the insane spiced with philosophical vitalism gained from his encounter with the Montpellier medical school. Gachet envisaged mental illness as that disruption in the harmony of body and mind which prevented the normal functioning of the "élan vital" or vital force.[3] Because of this disruption of the balance between mind and body, it was not unusual to find mental diseases accompanied by physical symptoms. However, Gachet felt that, in general, the prime symptom of mental illness was the patient's inability to function normally in society. Melancholia was, therefore, pathological sadness of such a degree that it inhibited a patient's ability to carry out the normal activities of everday life. However, Gachet viewed it as a wide syndrome which ranged from states perfectly compatible with an ambulatory status to severe forms of regressive dementia. In regard to the etiology of melancholia, Gachet was not impressed with the influence of organic factors. Instead, he felt that one must seek the causative forces within man's own relationships with his milieu and within man's own emotional structure.[4]

Gachet's system of therapy for melancholics was based on three principles: hospitalization, therapeutic activities, and psychological support. In regard to the first of these, Gachet felt that the hospital must provide a therapeutic milieu and must allow the patients as much freedom as possible, since the fear of incarceration was one of the most depressing of all worries. Second, mental and physical activities must be developed which would divert the patient's attention from his morbid preoccupations.[5] Finally, young Gachet felt that the physicians attending the patients should converse with the afflicted people, strive to determine what was at the basis of their problems, and attempt to reassure them. In the realm of physical modalities of therapy, Gachet allowed the use of warm baths to calm anxious patients, but he strongly condemned the still all too prevalent use of phlebotomy and purgation.

[2] Paul Gachet, *Le Docteur Gachet et Murer—Deux Amis des Impressionistes* (Paris, Editions des Musées Nationaux, 1956), 3–20.

[3] Paul-Ferdinand Gachet, *Etude sur la Mélancolie*, unpublished doctoral thesis, University of Montpellier, 1858. (All translations are by the author unless otherwise noted.)

[4] *Ibid.*, 23–26.

[5] *Ibid.*, 102.

Following establishment of a medical practice in Paris, Dr. Gachet again spoke out in regard to the problem of mental illness. A feature article had been published in the Parisian newspaper, "Le Figaro," suggesting that mental illness was contagious. Gachet, a very outspoken person on all topics, could not contain his fear that such a notion might set back for decades the work of the reformers. In a strongly worded letter to the editor, Dr. Gachet vigorously disputed the author's contention, pointing out the obvious—that if such were true, an epidemic of insanity should have occurred years earlier among the employees of the Salpêtrière.[6]

In 1875, after sixteen years in the practice of general medicine, which had also included the care of various mentally afflicted patients, Gachet published a third article. This time he spoke to a wide audience through the pages of a popular health annual to which he had been a regular contributor. Dr. Gachet now proclaimed that, contrary to a widely held opinion, insanity was not incurable and that, with the advent of further refinements in the humane treatment of the mentally ill, even more people might be returned to function in society. Once again, Dr. Gachet emphasized that "freedom is indispensable for a successful cure" and that the patient must be involved as much as possible in normal society while undergoing therapy. In addition, Gachet attacked the Law of 1838 which allowed almost unregulated confinement of patients thought to be mentally ill. He concluded by suggesting that the public would do well to divest itself of the idea that mental illness "is an exaggeration or a deviation of intelligence, that people who are taxed with originality are monomaniacs and are insane."[7]

The second reason that had led Theo Van Gogh to choose Gachet was that the doctor was himself an artist and had treated many artists as patients. While establishing a medical practice in the Latin Quarter of Paris, young Gachet also found time to perfect his ability as an engraver, and he contributed many engravings to a Parisian art magazine. Because of his reputation as a savant and wit, Gachet was invited to become a member of a literary society, *Les Eclectiques*[8], and he often embellished the society's announcements with his own humorous engravings.

Gachet was fascinated not only by creative art but also by the artistic mentality. In order to study the brains of these unusual personalities, he campaigned for the establishment of a Society for Mutual Autopsy. Unfortunately, Gachet's enthusiasm failed to convince many of his contemporaries. One of the first mental patients that Dr. Gachet worked with was the painter, Charles Méryon, who suffered from intermittent psychotic episodes and was also tormented by multiple phobias. Gachet interviewed Méryon on several occasions attempting to find the basis of his phobias, and during one interview he even secured permission to sketch him.[9] At the same time, through Camille Pissarro, the son of one of his oldest patients, the doctor was introduced into the circle of the Impressionist painters. Gachet loved their revolutionary techniques and had himself preached for years against the narrow style of the Academy. Just at the time when the Impressionists began to leave Paris in search of landscapes, Dr. Gachet purchased a country home at Auvers-sur-Oise, in the heart of one of the most picturesque areas. To his home in Auvers, Gachet invited men like Pissarro and Cézanne. There, they talked of painting, and Gachet offered medical care in return either for canvasses, which at that time were not selling well, or merely in exchange for the artists' companionship. Of all the artists of Pissarro's

[6] *Le Figaro*, August 18, 1859, 3.

[7] Paul-Ferdinand Gachet, "L'aliénation mentale," in *L'Annuaire de la Santé et de l'Hygiène*, 1875: 182–185.

[8] The *Société des Eclectiques* was one of many Parisian banquet societies whose membership was composed of prominent wits, intellectuals, and leaders of the liberal professions. These organizations appear to have developed out of the famous "campaign of banquets," organized in 1848 to foster support for the parliamentary movement attempting to oust Louis Philippe's unpopular premier, François Guizot (1781–1874).

[9] Paul Gachet, *Le Docteur Gachet et Murer . . .*, 30.

circle, Cézanne seems to have most fascinated Gachet. The doctor had met the artist's father years before, and he now invited the painter to spend some time in Auvers. Dr. Gachet was fascinated by the artist's recurrent nightmares and phobias, and he was also interested in his style of painting. Cézanne, in turn, seemed to thrive in Auvers, and he even sketched a portrait of the doctor.

During the succeeding years, Gachet's own reputation as an artist grew, and he himself exhibited regularly in the *Salon des Indépendants*.[10]

The most interesting encounter in the life of Dr. Gachet was that with Vincent Van Gogh. However, before looking into this episode, it is important to review several aspects of the artist's life. Van Gogh, the son of a strict Dutch Calvinist minister, had led a rather frustrating life, brightened only by his enthusiasm and genius for painting. From early in childhood until his untimely death, Vincent sustained a rather dependent relationship with his brother, Theo, the more conventional and stable of the two. After spending several years in Paris where he had studied the new developments in art, Vincent left for Arles in Provence in 1888. Here he entered what many art critics consider as his most fruitful period. Unfortunately, it was during this time that his behavior took a turn for the worse. Although he had suffered periods of great despondency in the past, Vincent now began to experience episodes during which he would do bizarre things, argue with his friends, and even become violent. After these episodes, he would fall into a deep sleep only to awaken without being able to remember what he had done.[11] Then, on Christmas Eve, 1888, in a fit of rage, he excised part of his ear and sent it to a young Arlesian prostitute. Following this episode, he was hospitalized only to be discharged and later readmitted after he had again experienced lapses of consciousness, now accompained by auditory hallucinations. It was the consensus of the physicians who attended him and of the artist himself that he was a sick man and that he should arrange a period of rest in a private hospital. Vincent chose the asylum of St. Remy, a private institution still in operation today, and located near the city of Arles.

The diagnosis of Van Gogh's illness remains an enigma to this day, despite an extensive literature devoted to the problem. Twentieth century historians of medicine diagnose Vincent as suffering either from psychomotor seizures, schizophrenia, or a psychopathological process of unknown etiology. In view of this, it is interesting that Dr. Rey, the intern who admitted Vincent to the hospital at Arles, diagnosed the artist's underlying problem as epilepsy, perhaps in part inspired by the work that a colleague was then doing on the syndrome of epilepsy without convulsions. In contrast, Dr. Urpar, the chief of service, made the diagnosis of acute mania with generalized delirium. Curiously, the admission diagnosis at the asylum of St. Remy combined the two, listing Vincent as suffering from "mania with terrifying auditory hallucinations and hereditary epilepsy."[12] Epilepsy and its various syndromes had fascinated many nineteenth century physicians, and the French literature contained many references to it. As early as 1838, Esquirol, a disciple of Pinel and a well known professor of psychiatry, had described what he called "epilepsy without convulsions," which was a behavioral syndrome that included recurrent episodes of bizarre activity. In 1862, Professor Trousseau of the Faculty of Medicine in Paris had written that certain types of abnormal behavior, including suicide and homocide could be caused by epilepsy alone.[13]

[10] The *Salon des Indépendants*, like the *Salon des Réfusés*, originated because the jury for the academic Salon continued in 1881 to reject the avant-garde artists. However, the impetus for the *Salon des Indépendants* came from the artists themselves, who founded a *Groupe des Artistes Indépendants*, pledged to exhibit regularly and to admit any painter who wished to join. Vincent Van Gogh, himself, later exhibited with the *Salon des Indépendants*.

[11] J. Hariga, "A propos de la psychologie de Van Gogh," in *Acta Neurologics et Psychiatrica Belgica*, 1959, **59**: 222.

[12] Jean Vinchon, "Diagnostic de la 'folie' de Van Gogh," in *Hist. med.*, Numero Special 1960: 23.

[13] K. G. Dahlgren, "Van Gogh als psychiatrisches problem," in *Confinia Psychiatrica*, 1959, **2**: 190–204.

While at St. Remy, Vincent established a friendly relationship with Dr. Peyron, the medical director and a retired naval physician. However, the artist continued to experience his intermittent episodes which were now followed by rather lengthy periods of depression. Yet, in between these periods, Vincent felt practically normal and began again to paint. Gradually, the attacks became less frequent, and Vincent begged his brother to arrange his departure. Dr. Peyron would only consider it if some type of medical supervision could be arranged. Theo learned of Dr. Gachet through the Pissarros, and shortly thereafter, met the physician at a dinner party. In a letter to Vincent, Theo conveyed his own first impression:

> I am very happy to tell you that I met Dr. Gachet. . . . He gives me the impression of being a man of understanding. Physically he is a little like you. . . . When I told him how your crisis came about, he said to me that he did not believe it had anything to do with madness, but that it was necessary for him to see you in order to be able to make a definite statement.[14]

Following the pleas of Vincent, Theo discussed the situation with Dr. Gachet and arranged for Vincent to go to the village of Auvers where he could be under the doctor's surveillance. Vincent was overjoyed and vowed that he would show Gachet that he was still capable of painting effectively. Fatally, however, a break in the proper chain of medical communications took place. Mysteriously, Dr. Peyron failed to spell out to Theo or to Gachet all the important details of Vincent's illness. And Theo himself failed to inform Gachet that Vincent had, on several occasions, attempted to commit suicide by ingesting paint and lamp oil.[15]

Vincent Van Gogh arrived in Paris on May 17, 1890, and appeared to be in robust health.[16] After several days as a guest in the home of his brother, the artist journeyed to Auvers where he met Dr. Gachet. The physician's plan was quite simple: Vincent was to live on his own in one of the village inns; however, he had a standing invitation to dine with the doctor and his family and to come to the Gachet house at any time to work or to talk and visit with the doctor. Dr. Gachet advised Vincent to live as simple a life as possible and to begin to paint again seriously. With only a brief interview to go on, Dr. Gachet had little upon which to base a diagnosis of the artist's condition, although he did feel that Vincent's obsessive habit of painting for long hours in the fiery Arlesian sun had contributed to the frequency of his spells. Dr. Gachet seems to have viewed Vincent's illness as more akin to epilepsy without convulsions complicated by periods of reactive depression. He was not convinced that Vincent suffered from pure insanity. His basic approach to the artist's problem was compatible with his own earlier writings on the moral treatment of the mentally afflicted. This included, of course, his particular beliefs in occupational therapy and in the necessity of freedom. Historically, Gachet's plan of therapy was perfectly adequate. Although the efficacy of bromide therapy was becoming known in the treatment of *grand mal* and *petit mal* epilepsy, its use in treating epilepsy without convulsions had not been substantiated. Therefore, in regard to this aspect of epilepsy, Gachet applied the formula of simple reassurance and suggestion which had been advocated years earlier by Professor Esquirol.[17]

[14] Theo Van Gogh to Vincent, March 29, 1890; see Vincent Van Gogh, *The Complete Letters of Vincent Van Gogh* (Greenwich: New York Graphic Society, 1959), volume III, #T 31, 567. All references will be to this edition of the letters, which will hereafter be cited as *Letters*.

[15] This information was, however, neatly recorded in the hospital ledger at St. Remy; see Edgar Leroy, "Le séjour de Vincent Van Gogh à l'asile de St. Remy-de-Provence," in *Aesculape*, 1926: 185–186.

[16] Johanna Van Gogh-Bonger, "Memoir of Vincent Van Gogh," in Vincent Van Gogh, *Letters*, volume I, L.

[17] Paul Gachet, *Le Docteur Gachet et Murer* . . ., 111. It is important to note that this system of treatment, *le régime moral*, had earlier been found by Esquirol to be as useful as anything else in the treatment of epilepsy. See: Owsei Temkin, *The Falling Sickness* (Baltimore: The Johns Hopkins Press, 1945), 281. During the latter decades of the century, the efficacy of bromide therapy in the treatment of *grand mal* and *petit mal* epilepsy was being increasingly studied.

Although Theo and Dr. Gachet were both optimistic in regard to Vincent's illness, the artist himself seems to have realized the seriousness of his own psychopathology. In addition, he even questioned the equilibrium of his friends. In a much quoted section from his letter to Theo of June the fourth, Vincent stated that Gachet "certainly seems to me as ill and distraught as you or I, and he is old and lost his wife several years ago, but he is very much the doctor, and his profession and faith still sustain him. We are great friends already."[18] Many art historians have naively interpreted this as evidence of Gachet's own profound mental illness. However, I feel it is a good deal more suggestive of Vincent's own difficulties in testing reality, although we must admit that Gachet was at times eccentric.

During the early weeks at Auvers, Vincent developed a warm and even therapeutic relationship with Dr. Gachet. The physician's knowledge and understanding of art was a major factor in the furthering of this relationship. Not only did Dr. Gachet teach Vincent to engrave, but he also encouraged the artist to work in his own familiar medium of oils. Vincent's esteem for Gachet is seen in the fact that his only engraving was a portrait of his mentor, and that shortly thereafter he completed the first of two portraits in oil of the old physician. In turn, Dr. Gachet was one of the few people who Vincent, himself, felt actually understood his paintings. In a letter to Theo, Vincent remarked about Gachet that "he has now got so far as to understand the last portrait of the *Arlésienne* . . . he always comes back to these portraits when he comes to see the studies and he understands them exactly, exactly I tell you, as they are."[19] At the same time, Vincent's letters also suggest that many of his own symptoms had subsided during the early weeks with Gachet. In his letter of June the tenth, he remarked that "all the same it is odd that here the nightmares have ceased to such an extent."[20]

However, as June drew to a close, Vincent again became depressed and attempted to discuss his feelings with Gachet. In another letter to Theo and his wife, the artist wrote that "if the melancholy or anything else became too much for me to bear, he (Gachet) could easily do something to lessen its intensity; he said that I must not feel awkward about being frank with him."[21] Then, early in July, Van Gogh had what may have been his only episode to which Gachet was witness. One evening the two men were in the midst of a lively discussion over the merits of an oil painting by Guillaumin. Vincent loved this work and was angry that Gachet had not yet had it framed. Suddenly, Vincent apparently became quite agitated and threatened Gachet physically, while yelling at him in Dutch. The doctor remained completely calm, and Vincent left, only to return the next morning, acting as if nothing at all had happened the night before.[22] Unfortunately, this episode marked a turning point in the relationship between the two. After this, they remained on friendly terms, but Vincent was unable to express to Gachet his renewed feelings of isolation and depression.

Instead the artist poured out his suppressed feelings onto canvas, painting in an almost frenzied manner. He turned out canvas after canvas, but apparently without satisfying himself. In a letter to Theo, Vincent described a canvas which he was painting, and at the same time, he suggested the depths of his own depression. "There are vast fields of wheat under

See: Wilder G. Penfield, *Epilepsy* (Baltimore: Charles C Thomas, 1941), 490.

[18] Vincent to Theo, June 4, 1890; see Vincent Van Gogh, *Letters*, volume III, 276.

[19] Vincent to Theo, June 4, 1890; see Vincent Van Gogh, *Letters*, volume III, 276 f.

[20] Vincent to Theo, June 10, 1890; see Vincent Van Gogh, *Letters*, volume III, 280.

[21] Vincent to Theo and Jo, early June, 1890; see Vincent Van Gogh, *Letters*, volume III, 275. This strongly suggests that both Van Gogh and Gachet were aware of the former's feelings of depression and that this was a topic of conversation.

[22] Victor Doiteau, "La curieuse figure du Docteur Gachet," in *Aesculape*, 1923: 278–279. Gachet here followed the advice of the pioneers in the "moral treatment" of the insane, who suggested that only by remaining calm could the physician expect his patients to regain control of themselves.

troubled skies, and I did not need to go out of my way to try to express sadness and extreme loneliness."[23]

Unknown to Dr. Gachet, Van Gogh had removed an old pistol from the hunting sack of one of the boys from the nearby countryside.[24] Several days later, on July the twenty-seventh, while painting in the wheat fields above Auvers, Vincent attempted to commit suicide by shooting himself in the chest. Immediately unsuccessful, he dragged himself to his inn where the landlord sent for Dr. Gachet and for another physician.

According to Gachet's son, Paul, the old doctor was taken by surprise. He rushed to the inn and, upon examining Van Gogh, found that the missile had been deflected by the fifth rib and had descended inferiorly, probably ending in the area of the left lower quadrant.[25] The two physicians then consulted and decided that, in view of what surgery had to offer, it was useless to attempt to transport Vincent to Paris. Thus began the long vigil. The old doctor summoned Theo, and, while awaiting his arrival, he sat by Vincent's side. He began to smoke and, while Van Gogh slept, finished a sketch of the artist on his deathbed. The following day, Theo arrived, and early in the morning of the twenty-ninth, Vincent Van Gogh quietly died. After a great deal of discussion, Gachet persuaded the village priest to make an exception and to allow this victim of suicide to be buried in the cemetery, not far from the artist's own "vast fields of wheat."[26]

In retrospect, Gachet's encounter with Van Gogh had been most unusual, for it combined the intricacies of the doctor-patient relationship with the complexities of the rapport between two artists. It seems reasonable, from the fervor with which Gachet later worked to preserve the memory of Van Gogh, that the doctor felt in some part responsible for Vincent's death, which he had failed to prevent through hospitalization or greater surveillance. And yet, in defense of Gachet, it should be remembered that from what information he had received as to Van Gogh's earlier problems, the diagnosis seemed primarily that of epilepsy without convulsions. The artist himself appears to have concealed a good part of his own depression from the doctor. Therefore, Gachet's program of general humane treatment, occupational activities, and frequent meetings seemed perfectly acceptable as therapy.

Dr. Gachet was a unique and individualistic personality. He was fascinated by the problem of mental illness and attempted to work with distressed patients at a time when most physicians had barely begun to accept the therapeutic possibilities of psychiatry. In addition, Gachet was an artist and was fascinated by the artistic mentality. He treated, aided, and encouraged many of the Impressionists long before these artists received any public acclaim. Without a doubt, his most famous patient was Vincent Van Gogh, an artistic genius whose illness is poorly understood even today. Between the two men there developed a unique relationship, at times strictly artistic and at times therapeutic. For the historian of medicine, it is necessary to pay homage to an artist, to Vincent Van Gogh, for in his extraordinary portraits of his last physician, he has preserved much of that curious and fascinating man: Dr. Paul-Ferdinand Gachet.

[23] Vincent to Theo and Jo, early July, 1890; see Vincent Van Gogh, *Letters*, volume III, 295.

[24] Victor Doiteau, "Deux copains de Van Gogh," in *Aesculape*, March, 1957: 46.

[25] Paul Gachet, "Les médecins de Théodore et Vincent Van Gogh," in *Aesculape*, March, 1957: 27.

[26] *Ibid.*, 34.

Memoir of Albert Schweitzer (1875–1965)*

By FRED B. ROGERS, M.D.

DR. ALBERT SCHWEITZER, an honorary fellow of this College, died on 4 September 1965, at Lambaréné, Gabon, West Africa, at age ninety after a short illness. Attaining distinction early as a theologian, philosopher and musician, he labored during the last fifty years of his life as a physician, devoted to the practical needs of his patients. His long and useful career was one rich in deeds and thought. It had some aspects of a miracle and his achievements an epic quality. A man of peace and good will, he will long be admired and emulated.

Albert Louis Philipp Schweitzer was born on 14 January 1875, the son of a Protestant minister, in the upper Alsatian town of Kaysersberg. Soon afterwards the family moved to Gunsbach, fifteen miles away, which was Schweitzer's European home during his missionary service. His native land, Alsace, the pawn of two countries, changed allegiance between Germany and France several times during his lifetime. As a result, he was bilingual and cosmopolitan in outlook.

Talented in music like his parents, Albert began piano lessons at five and composed harmonies for hymns at seven; at eight he began to play the organ and a year later accompanied services at the parish church. After classical schooling at Mulhouse, he entered Strasbourg University in 1893, aiming for degrees in theology and philosophy. His university course was interrupted by a term of military service in the German army, during which period he studied a Greek New Testament carried in his knapsack. About this time he became a pupil of the great Parisian organist, Widor, studied music and philosophy in Berlin, and devoted himself to organ building and the preservation of old pipe organs.

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After receiving a doctorate in philosophy, a licentiate in theology, and being ordained to the Lutheran ministry, he was named principal of the College of St. Thomas, a theological seminary of Strasbourg University. Deciding to dedicate himself to the "direct service of humanity" at age thirty, in 1906 he began to study medicine, paying his tuition through publication royalties and organ recitals. He received his doctorate in medicine at Strasbourg in February, 1913, and promptly offered his services to the Paris Missionary Society. In the preceding year he had married Hélène Bresslau, the daughter of a Jewish history professor at the University. Having trained as a nurse, she was a helpmate in his medical, musical and literary work.

Following a course in tropical medicine taken in Paris, the Schweitzers sailed from Bordeaux in the spring of 1913 for the African mission station at Lambaréné, deep in the forests of Gabon, fifty miles south of the Equator. They took along seventy packing cases of surgical and tropical equipment to this remote outpost. The luggage also included a piano with organ pedal attachments. A gift of the Paris Bach Society, it was lined with zinc to resist the ravages of heat, moisture and insects.

When Dr. Schweitzer reached the banks of the Ogowé River in Gabon he found little to call a hospital. His first operating room was in a converted hen-house. During the initial year in Africa he treated over 2000 patients, the majority of them suffering from tropical diseases—malaria, sleeping sickness, dysentery, leprosy. The rival tribes around Lambaréné, the Fangs and Galoas, had their own languages, customs and witch doctors. In this perilous setting Schweitzer conducted a general medical practice with the aid of his wife and African helpers such as the talented Joseph Azoawami. Among his primitive patients he was called *Oganga*, the medicine man, and here he worked

from 1913 to 1917, in the humid jungle, the worst climate in the world.

During World War I the Doctor and his wife, being German aliens in French territory, were sent to an internment camp in France. Here he compiled an account of his work at Lambaréné, *On the Edge of the Primeval Forest*, which was published in 1922. In this book he noted:

> On the whole I feel that the primitive man is much more good natured than we Europeans are; with Christianity added to his good qualities, wonderfully noble characters can result. I expect that I am not the only white man who feels himself put to shame by the natives.

Also, while in confinement, Schweitzer prepared a draft of his great work, *The Philosophy of Civilization*, the first volume of which appeared in 1923. In the following year he returned to Lambaréné, accompanied by Noel Gillespie, an Oxford medical student, and several Swiss and French nurses. These coworkers were among a volunteer group of dedicated persons who have since staffed the hospital. A new hospital was completed in 1927, in a healthier location two miles upstream from the old one—which had been largely reclaimed by the jungle in the interim. Access to the site was by dugout canoe, there then being no roads in the vicinity.*

The hospital-village, in 1965, has 500 beds and is a complex of seventy-two buildings covering 225 acres. Large numbers of Gabonese out-patients are also accommodated—up to 200 at any given time. Supported by donations, the staff now includes six doctors and fifteen nurses from Europe, eighteen native nurses and thirty to fifty orderlies and translators. About 800 surgical operations, many for the repair of hernias, and numerous obstetrical deliveries are performed each year.† Problems of housing, feeding and sanitation under jungle conditions, with limited funds, require extraordinary patience and ingenuity. Dr. Walter E. Munz, a Swiss physician, assumed general direction of the hospital early in 1965.

The treatment of lepers at Lambaréné has made medical history. At the outset, Schweitzer's hospital was the only one in a vast region which provided modern methods for the treatment of leprosy, and patients came there from as far away as 600 miles. At present, Dr. Isao Takahashi, a Japanese physician who has worked in leprosaria in the Far East, is in charge of this activity. Using the $33,000 Nobel Peace Prize money awarded him in 1952, Dr. Schweitzer constructed a new village about one half mile from the main hospital for the care of 250 leprous patients. An improved radiography unit was also installed at the hospital then.

Though criticized on the grounds that his hospital lacked the administrative efficiency and hygienic standards of non-tropical, metropolitan centers, he countered the criticism by claiming that methods must be adapted to the prevailing conditions. Professional services are dispensed, he added, in a setting familiar to the patients and their families. A friendly menagerie of animals and birds roams at will, attesting to their host's respect for all life. The ethical philosophy of "reverence for life" came in part as a reaction to wanton slaughter of wildlife in Africa. Dr. Schweitzer summed up his *credo* by saying: "The purpose of human life is to serve and to show compassion and the will to help others." Inscribed on the lamp outside the hospital are the following words of welcome: "Here, at whatever hour you come, you will find light and help and human kindness."

In his theological writings, Schweitzer attempted to extricate the "real Jesus" from the Gospel Christ. His book, *The Quest of the Historical Jesus*, published in 1911, was a milestone in modern theology. Later works, *Paul and his Interpreters* (1912), *The Mystery of the Kingdom of God* (1914), *Christianity and*

* Albert Schweitzer: *Medicine in the Jungle*, Journal of the American Medical Association *156:* 1547–1549, Dec. 25, 1954.

† Robert M. Goldwyn and Richard L. Friedman: *Surgery at the Albert Schweitzer Hospital, Lambaréné, Gabon*, New England Journal of Medicine 264: 1031–1033, May 18, 1961.

the Religions of the World (1923), *The Mysticism of Paul the Apostle* (1931), and *Indian Thought and its Development* (1936) also reveal his breadth of scholarship. In his *Memoirs of Childhood and Youth* (1924) he wrote:

> When I was still a child it impressed me as something beautiful that in our village, Catholics and Protestants worshipped God in the same church. . . . I would like to wish that all churches which are still common to both religious groups in Alsace would be retained as such, as a prophecy and a reminder of a future in religious unity, about which we should be ever mindful if we are truly Christians.

On Schweitzer's passing, Maurice Cardinal Feltin, Archbishop of Paris, said: "His life and work shall long stand out as an eloquent testimony to the charity of Christ and a call for true love among men." Michael Ramsey, Archbishop of Canterbury, added: "Albert Schweitzer was one of the great Christians of our time, or of any time."

In the realm of music, Schweitzer's importance to the art is secure and lasting. His interpretive biography, *Jean Sebastian Bach, le Musicien-Poète*, published in 1905, provided new insights into the composer's work. Reissued three years later in German, the much enlarged book was translated into English in 1911 under the title, *J. S. Bach*. "To read Schweitzer's *Bach*", wrote Widor, "is not only to get to know the composer and his work, but to penetrate also into the essence of music in general."

In 1935, Dr. Schweitzer recorded a Bach recital at All Hallows Church, London. This album, now available on an Angel *LP* disc, reveals his performing style at its best. In the following year he made records of organ music for Columbia Records (London), playing at St. Aurelia's Church in Strasbourg. These recordings recall Robert Schumann's comment after hearing Felix Mendelssohn perform Bach at Leipzig in 1840: "There is nothing greater in music than the enjoyment of the twofold mastery displayed when one master expresses the other."

In 1951, Albert Schweitzer recorded six *LP* volumes of Bach works, using the organ at the Parish Church in Gunsbach. These volumes, issued by Columbia Masterworks, contain special notes written by Dr. Schweitzer and translated by Nathan Broder. Mr. Broder has said: "These albums together with their elaborate notes remain affecting mementoes of the great humanitarian's lifelong reverence for his favorite composer." Also in 1951, Schweitzer recorded for Columbia César Franck's *Trois Chorals pour Orgue*, again with notes written to expound the musical score. Other discs recorded Mendelssohn's Organ Sonatas No. 4 in B Flat Major and No. 6 in D Minor and Widor's Organ Symphony No. 6 in G Minor, all with commentary by the performer.

Another valuable contribution was a standard edition of Bach's complete organ works, begun in collaboration with his mentor, Widor, and continued with an Alsatian colleague, Nies-Berger, now an organist in the United States. So far six volumes have appeared; it is fortunate that the remaining two volumes were completed at the time of Schweitzer's death. The text is in three languages—German, French and English—with expository prefaces to guide the player. (*J. S. Bach: Complete Organ Works. A Critico-Practical Edition in Eight Volumes.* G. Schirmer Inc., New York. Vols. I–IV: *Preludes and Fugues*; 1913; Vol. V: *Concertos and Sonatas*; Vol. VI: *Various Choral Compositions*, 1954. Vols. I–V edited by Albert Schweitzer and Charles-Marie Widor; Vol. VI edited by Édouard Nies-Berger and Albert Schweitzer.)

Dr. Schweitzer returned to Europe several times between the two world wars. During 1919–21, he worked as a physician at the City Hospital of Strasbourg and resumed his former position as preacher at St. Nicholas' Church in that city. Concerts and lectures helped to raise funds, his writings won ever wider support, and by 1932 his African hospital was safely if modestly established. The "discovery" of his work at Lambaréné by the press when war again threatened his mission in the 1940's was a mixed blessing for *le grand docteur*. He welcomed ever-increasing

numbers of visitors, from many ranks and many lands, to the jungle hospital.

In 1949, Schweitzer participated in the Goethe bicentenary celebrations in Europe and the United States. He spent the month of July visiting Aspen, Colorado, Chicago, New York, and Boston, after which he returned to his home in France. In 1950 he was made a Chevalier of the Legion of Honor.

The first Paracelsus Medal of the German Physicians Congress was awarded to Dr. Schweitzer in 1952 for outstanding service. In the same year he became a member of the French Academy of Moral and Political Sciences, and two years later was made an honorary member of the American Academy of Arts and Sciences.

In 1955 he received the honorary membership of the Order of Merit from Queen Elizabeth II, and was made an honorary fellow of the Royal Society of Medicine and of the Royal Society of Tropical Medicine and Hygiene. Following the detonations of atomic bombs, he spoke out forcefully against nuclear weapons; his Nobel Peace Prize address, delivered at Oslo, Norway, in 1954, was entitled, *The Problem of Peace.* Four years later this address was revised as a declaration, *Peace or Atomic War?*

In 1962, upon election to honorary fellowship in The College of Physicians of Philadelphia, he wrote to President Thomas M. Durant: "I appreciate the great honor that you have bestowed upon me. . . . Please convey my gratitude to all members of the organization . . . it is very fine that I am able to be in spiritual contact with you." Dr. Schweitzer received honorary degrees from the universities of Zürich, Prague, Edinburgh, Oxford, St. Andrews, Chicago, Tübingen, Cambridge and Capetown.

Albert Schweitzer's altruism set a vibratory example that unlocked goodness in others. Seven hospitals, in various parts of the world, now honor his name: Dr. Larimer Mellon's in the Artibonite Valley in Haiti; Dr. Theodor Binder's Hospital Amazonico Albert Schweitzer at Pucallpa, Peru; Dr. Gaine Cannon's in Balsam Grove, North Carolina; Dr. Humberto Sa's in Guarapuana, Brazil; Dr. Timothy Rhe's on an island off Korea; Dr. Michael Wood's in Kenya, East Africa; and Dr. Van Aswegan's in Basutoland, South Africa. Clinics, orphanages, schools, colleges and professorships in countries around the globe bear his name and extend his philosophy. The Albert Schweitzer Chair in the Humanities at New York University and the Albert Schweitzer Elementary School at Levittown, Pa., are nearby examples.

Madame Schweitzer, described by her husband as "the most loyal of comrades", died on 5 July 1957, at age seventy-nine. Her remains now rest beside those of her spouse at Lambaréné. Their daughter, Rhena, born on the doctor's birthday in 1919, grew up in Europe and married Jean Eckert, an organ builder in Zürich, Switzerland. Recently she has worked for several months each year at her father's hospital. Her oldest daughter, Monique, now has a son of her own. A second daughter, Christiane, is studying medicine, and a third, Katrine, is gifted in music. A son, Philipp, is an organ builder like his father.

Dr. Dana L. Farnsworth of Harvard University, in 1962, summarized the meaning of Albert Schweitzer's life to medicine.‡ He expressed the esteem with which the medical profession regarded this paradigm and "first citizen of the world":

> Schweitzer chose medicine deliberately, after major accomplishments in three other fields, because he felt that any person of unusual attainments and potential happiness owed a great deal to those not so fortunate. . . . The meaning of Dr. Schweitzer's life to medicine is that the single example of a brilliant man giving himself in service to others less fortunate than himself serves as a stimulus to millions of others. . . . Dr. Schweitzer has exemplified in his own life the need for a thoughtful blend of intelligence, compassion, responbility and unselfishness, all compatible with the enjoyment of life in its manifold aspects.

‡ Dana L. Farnsworth: *The Meaning of Albert Schweitzer's Life to Medicine,* pp. 280–291; in A. A. Roback (ed.), *In Albert Schweitzer's Realms; A Symposium,* Sci-Art Publishers, Cambridge, Mass., 1962.

Memoir of Roy W. Mohler (1892–1964)*

By JOHN B. MONTGOMERY, M.D.

ROY WILLIAM MOHLER, a Fellow of this College for thirty-two years, died on August 8, 1964, as the result of progressive cardiac and renal failure, five weeks after the successful resection of an aneurysm of the abdominal aorta.

Born in Mount Holly Springs, Pa., on December 26, 1892, the son of John Wesley and Ella Keefer Mohler, Roy Mohler was educated in the local public schools, Conway Hall and Dickinson College, where he received his A.B. degree in June, 1917. He matriculated at Jefferson Medical College of Philadelphia in September 1917 and joined The Student Army Training Corps. After receiving his M.D. degree in 1921, Dr. Mohler was appointed first lieutenant in the Medical Officers Reserve Corps of the United States Army. Dickinson College granted him the M.A. degree during the same year.

Following an internship at the Bryn Mawr Hospital, Dr. Mohler opened his office in Philadelphia and became associated with the late Dr. Brooke M. Anspach, Professor of Gynecology in Jefferson Medical College. After a period of preliminary training he became clinical pathologist and anesthetist to the Department of Gynecology. From these early associations Dr. Mohler developed a sense of responsibility to medical education and to Jefferson Medical College that continued with increasing intensity throughout his entire career.

Numerous addresses and papers on a variety of clinical subjects brought him wide recognition as a teacher and a clinical investigator. A serious student and an enthusiastic clinical teacher, he rose through the ranks to become Clinical Professor of Obstetrics and Gynecology. In his later years and in semi-retirement, he served as coordinator of the House Staff Educational Program at the Jefferson Medical College Hospital.

On November 11, 1926, Dr. Mohler married Isabelle Blackburn of Williamsport, Pa. They have one child, Barbara, now Mrs. John H. McIlvaine, Jr.

In 1930, while maintaining his teaching position at Jefferson, Dr. Mohler accepted an appointment at The Philadelphia Lying-in-Hospital, a division of the Pennsylvania Hospital, where he served under the late Dr. Norris W. Vaux. During the war years, when Dr. Vaux's staff was reduced in numbers, Dr. Mohler put forth intense personal effort in helping to maintain the high quality of Ward and Out-Patient Services.

Dr. Mohler resigned from the Pennsylvania Hospital in 1947, following his appointment as Chief of Obstetrics and Gynecology at the Methodist Episcopal Hospital of Philadelphia, where he had been a member of the Staff since 1936. He became a tower of strength in the medical affairs of this fine old Institution and under his guidance an approved residency training program was developed in the Department of Obstetrics and Gynecology, and an active teaching affiliation was established with Jefferson Medical College, involving Medicine and Surgery, as well as Obstetrics and Gynecology. On his retirement in 1957, he continued to serve as a member of the Board of Trustees of the Methodist Hospital.

Dr. Mohler had a deep interest in the problems of organized medicine. He served on the Board of Directors of the Philadelphia County Medical Society, was Vice-President from 1942–1945, and represented the Society in the House of Delegates of the Pennsylvania Medical Society for many years. He was an early supporter of Blue Cross and Blue Shield. Elected to the original Board of Directors of

* Read before The College of Physicians of Philadelphia, 7 April 1965. Prepared and published at the request of the Council of The College of Physicians of Philadelphia.

the Medical Service Association of Pennsylvania, he became a member of the Executive Committee, which he served with foresight and dedication until the time of his death.

Dr. Mohler was a devoted Alumnus of Dickinson College, from which he received the honorary degree of Doctor of Science in 1943. He was a member of its Board of Trustees and its Executive Committee. One of his proudest claims was that his daughter was a Dickinson Alumna. He had a great concern for young men entering the medical profession. Many received the benefit of his helpful interest, inspiration and guidance.

Dr. Mohler was a past president of the Obstetrical Society of Philadelphia. He was a Diplomate of the American Board of Obstetrics and Gynecology; a Fellow of the American College of Obstetricians and Gynecologists, and a Fellow of the American College of Surgeons. He was proud of his membership in the Rotary Club of Philadelphia. His loyalty to his Medical Alma Mater was expressed by many years of service on the Executive Committee of the Jefferson Medical College Alumni Association. In 1944 Dr. Mohler was elected to Fellowship in the American Association of Obstetricians and Gynecologists. He prized this honor highly and never missed an annual meeting, where he formed many friendships.

Distinguished by a deep loyalty to medicine, possessed of an inquiring and discriminating mind and a compelling desire for service to his fellow man, Roy Mohler was always guided by intellectual honesty and the courage of his convictions. Respected by his colleagues, his devotion to a high quality of medical practice and his warm personal interest made him the beloved physician to a host of loyal patients.

Memoir of Charles E. G. Shannon (1875–1965)*

By SIDNEY G. RADBILL, M.D.

CHARLES EMERY GOULD SHANNON was born on September 16, 1875 at Saco, Maine, the son of Professor Charles Way and Mary Emery Shannon.

He was one of over a thousand descendants of Robert Gould who came to Massachusetts in 1623. After he graduated from Colby College at Waterville, Maine, with the B.A. degree, he was encouraged by his cousin George M. Gould, an ophthalmologist of note and widely-known author of Philadelphia, to pursue the study of medicine. Entering Jefferson Medical College he received his degree of Doctor of Medicine three years later, in 1902; and after an internship at the Pottsville Hospital, matriculated at Harvard Medical School for a special post-graduate course in ophthalmology at the Massachusetts Eye and Ear Infirmary. On his return to Philadelphia he was invited by Dr. Howard F. Hansell, who was at that time Professor of Ophthalmology at Jefferson Medical College, to become his assistant both in his office and at the Jefferson Hospital. In the course of time Doctor Shannon then became chief of the Eye Department at the Hospital and associate in Ophthalmology at Jefferson Medical College.

In 1911 he received the appointment of assistant ophthalmologist to the Philadelphia General Hospital, and when Dr. Hansell resigned in 1919, was appointed in his place as attending ophthalmologist at that institution. Following the death of the Professor of Ophthalmology, William M. Sweet, in 1927, Doctor Shannon was elected to succeed him in the chair at Jefferson Medical College. In 1908 he was elected a Fellow of the College of Physicians of Philadelphia, and among a number of important contributions which he made to the ophthalmological literature was a memoir of Dr. Howard Forde Hansell, in 1935, for this College. He was also a member of the Philadelphia County Medical Society, the Pennsylvania Medical Society, the American Academy of Ophthalmology, the Section on Ophthalmology of the College of Physicians and other groups in his special field. He also held membership in the Sons of the American Revolution and belonged to two Greek letter fraternities, the Delta Kappa Epsilon and the Phi Alpha Sigma.

Doctor Shannon was a quiet, soft spoken gentleman with a delightful sense of humor. A devoted and loyal son of Jefferson Medical College, he was loved alike by his associates and his students. After his last lecture in the clinical amphitheatre at Jefferson on May 7, 1948, the members of the senior class of 1948 presented him with a beautiful watch and a splendid oil portrait for which he had posed at the request of the class. This portrait now hangs in a large hall at the Jefferson Medical College.

On October 5, 1910, Doctor Shannon was married to A. Gertrude Webber of Waterville, Maine. Upon retiring from practice in 1948 he moved to Waterville and there resumed the practice of ophthalmology. During the graduation exercises in June, 1954, Colby College awarded him the honorary degree of Sc.D., a well deserved and fitting tribute to a distinguished alumnus. He died February 2, 1965 at his residence, 9 Park Street, Waterville, at the age of 89. He will long be remembered by his many former pupils and friends.

* Prepared and published at the request of the Council of The College of Physicians of Philadelphia.

Memoir of Norman Merle MacNeill (1886–1965)*

By EDWARD LOUIS BAUER, M.D.

THERE are many facets in the life of Doctor Norman Merle MacNeill that reflect a brilliant light like a perfectly cut diamond. While he served well his native land, his home of adoption was the chief beneficiary of his activities. He was born on December 12, 1886 in Grand Narrows, Nova Scotia (New Scotland). His ancestors were pure Scot of an honorable and celebrated clan. He was of the third generation in Nova Scotia but he could read, write and speak Gaelic fluently, perhaps the most difficult of western European languages, and impeccable English without a burr.

Dr. MacNeill attended St. Francis Xavier University in Nova Scotia during 1903–04, combining an arts and a premedical course. This course was complemented by one in nurses' training. Immediately thereupon (1912) he enrolled in the Jefferson Medical College in Philadelphia from which he graduated in the spring of 1916. The next step was a rotating internship in St. Joseph's Hospital in Philadelphia of one year's duration. That was the year 1917 when the United States entered World War I. Not having his second naturalization papers he was ineligible for a commission in the United States Army. He passed his Pennsylvania State Board examination and then returning to Canada received a Captain's commission in the Canadian contingent of the British Army. He was sent abroad immediately. In England his duties were to act as physician to officers, nurses and their staffs as well as to police their sanitary surroundings. These same duties were later assigned to him in France where his field was greatly expanded.

At the expiration of the war the western world was in the throes of a catastrophic epidemic of influenza. Ships were impressed to transport the sick to Canada with the hope that these troops would be better cared for at home. Dr. MacNeill was apparently immune to this scourge and was made ranking officer on one of these overcrowded vessels. Fresh air and sunshine aided him in his meticulous attention to his patients and his mortality rate was very low. His case records were excellent and indicated a keen clinical study of each individual patient. After this severe trial, when called upon in discussion, he modestly but authoritatively added much to a clearer understanding of the behavior of this infection.

Upon his discharge from the Army in 1919 he returned to Philadelphia and made it his permanent home. The Pennsylvania Hospital for Mental Diseases in West Philadelphia found a place for him as a Resident Physician. This institution had as its "guests" a large proportion of patients on the private service and this was a challenge. It took tact and an extraordinary curiosity to fathom the cause of mental illness and after careful study Dr. MacNeill became convinced that early environment had much to do with the instability of these minds with which he was dealing. He decided to study at first hand the young mind as it was possibly traumatized. He resigned his Residency in 1921. As a field for the study of children he applied for a place in the Outpatient Pediatric Department of the Jefferson Medical College and Hospital.

Professor Edwin E. Graham appointed Dr. MacNeill as an Assistant in the Outpatient Department, although he was aware that Dr. MacNeill had had no post graduate training in Pediatrics nor did he probably inquire as to what prompted him to apply. This latest addition to the Pediatric Staff was not a

* Prepared and published with the approval of the Council of The College of Physicians of Philadelphia.

novitiate for long. His natural curiosity led him to indulge in many hours of reading the pediatric literature and to regularly attend the pediatric meetings. These profitably augmented his clinical experiences. He was among the first to qualify as a Diplomate before the American Board of Pediatrics in 1937. Naturally his psychiatric and psychologic studies continued but without the immediate help of his confreres.

Professor Graham resigned in 1926 and his successor in liaison with the Department of Neurology opened in that year the first pediatric clinic for disturbed children and their mental problems in a general hospital. The general clinic and the teaching program were reorganized and Dr. MacNeill was appointed Chief of Clinic and was ever in the foreground in a loyal service that lasted throughout this and subsequent administrations. His correlation with the aforementioned clinics as well as other new divisional clinics worked for an harmonious unit. As a pedagogue he was unique in many ways. The students respected his erudition but loved him for his down to earth methods of presentation. He rose through the college ranks to become in 1951 Clinical Professor of Pediatrics. The entire departmental standards were enhanced by his devotion to his service.

When the United States entered World War II this long naturalized citizen applied for a commission in the American Expeditionary Force. It was indeed a well deserved recognition of his chosen life's work that the Recruiting Board told him to return to his babies and minister to them. He did find time to aid the distressed seamen of the land of his nativity in Philadelphia. For this and his World War I service, King George V of Great Britain, in 1948, gave him a gold medal.

He was active in the Phi Rho Sigma Medical Fraternity and was national chairman of its student loan fund. Other extra curricular activities included his founding of the Pasteur Medical Society and of the Nurses' Guild. In his absence at a special meeting the latter adopted the name of "The Norman Merle MacNeill Nurses' Guild." These two Catholic Societies functioned as one. They operated essentially in like manner as the Y.M.C.A. and the Y.W.C.A. but with a denominational religious motif.

Dr. MacNeill resigned as Pediatrist from the Staff of St. Joseph's Hospital after a brief service and later was welcomed to the Pediatric Staff of Nazareth Hospital and served it in harmony until his death. This service provided a happy liaison with Jefferson Hospital. As Attending Pediatrist at the Philadelphia Hospital for Contagious Diseases from 1931 to 1958 he demonstrated the clinical aspects of the acute infectious diseases in childhood to the Junior Class of Jefferson Medical College until practically all of these conditions became so rare that none were available on scheduled days. As Assistant Physician, 1932 to 1965, to the Girard College, a private boarding school for poor white orphan boys, he was very popular. This school was founded by an early wealthy Philadelphian, Stephen Girard. It has always maintained the highest educational and medical standards found in any primary and secondary school at no cost to the student. Dr. MacNeill was also the Pediatrist to the Simons Mission Settlement.

In Denver, Colorado, in 1961, he was chosen as National Catholic Doctor of the Year by the National Federation of Catholic Physicians. Another recognition was a plaque in his honor placed on the wall of the pediatric classroom in Jefferson Hospital by his associates in the Department. He retired from Jefferson in 1964 as Clinical Professor of Pediatrics (Honorary).

Dr. MacNeill was a past president of the American Catholic Historical Society and was also a distinguished member of the British Officers Club serving a term as its president. He was active as a Fellow in several learned medical societies, among them the College of Physicians of Philadelphia, the American Academy of Pediatrics, the American Medical Association and its affiliated subdivisions and the Philadelphia Pediatrics Society.

How could a man with all these irons in the fire make a living in the practice of Pediatrics? He never received any emolument from Jefferson or his other hospitals save a small fee from Girard College. He had a large private practice, especially in his office, and he responded to night calls. He never named or asked for a fee. He never sent bills and was embarrassed when a patient asked his fee, accepting only that which was laid on his desk. Often he was known to say, "No, no, that is too much", and push part of it back and if he knew that the patient was poor he would not accept any of it. This is not a rumor for dozens of his patients have told of this experience in affectionate gratitude.

This truly dedicated Doctor of Medicine and beloved friend obeyed the ethics of his Hippocratic Oath and his Christian vows with no deviation and passed to his eternal rest in the early morning of June 16, 1965.

"Blessed are the pure in heart, for they shall see God."

Matthew 5:8

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Presidential Address: The College of Physicians of Philadelphia[1]

By JOHN H. GIBBON, Jr., M.D., SC.D. (HON.)

FELLOWS of the College and guests: It is my pleasant duty to report to you again concerning matters of interest and importance to the College that have occurred during the past year.

The Fellows

For the past few years, the recruitment and scanning of candidates for fellowship has been carried out by the devoted labor of the Membership Committee under the able chairmanship of Dr. Katharine R. Sturgis. During the past year, fifty new Fellows were elected, slightly more than making up for the losses due to the ravages of time and other causes. As of January 1 this year, we had 1,087 Resident Fellows and 158 Non-resident Fellows, making a total of 1,245 not including our eight Honorary Fellows and three Honorary Associates. Subtracting from these figures the number of Fellows with life membership and those whose dues have been remitted by Council, there were 982 dues-paying Resident Fellows (an increase of nine over January 1, 1965) and 130 Non-resident Fellows (the same as last year). We must, of course, continue to elicit the interest of qualified physicians residing in Philadelphia and its vicinity to support the College by joining the ranks of its Fellows and participating in its activities.

The Library

I am sure that you are all aware that the Health Sciences Library Assistance Act of 1965 has passed the Congress and has been signed by the President. As yet no appropriations have been passed to implement the bill. Hopefully, a suitable appropriation for this purpose will be recommended by the President in the budget he will present to the Congress. Fellows can be assured that the Library Committee, our Librarian, our Honorary Librarian, your Officers and Council have taken all necessary steps so that the Library of The College of Physicians of Philadelphia may receive Federal assistance and presumably be designated the Regional Medical Library for this geographic area.

The work of the Library has continued to grow during the past year. The total number of currently received serials has risen from 3,121 last year to 3,210 this year. In all other areas of activity the work of the Library has also increased. Our present stack space will probably be exhausted

[1] Annual Report of the President, The College of Physicians of Philadelphia, 5 January 1966.

before 1975 and, prior to that date, two new stories should be added to the existing structure to provide for future expansion. These additional floors have been estimated to cost over half a million dollars. A more exact estimate of the cost of these floors will be developed by the Library Committee during the current year. The Finance Committee will also explore all possible sources of support for such a capital expenditure, including the Federal Government. For other details concerning the many activities of the Library, I refer the Fellows to the Librarian's report for the year 1965, which will be published in the April issue of the *Transactions & Studies of The College of Physicians of Philadelphia.*

Reception at the Philadelphia Museum of Art

The special exhibition of "The Art of Philadelphia Medicine" at the Philadelphia Museum of Art in the Fall of 1965 provided an excellent opportunity for a gala social occasion for the Fellows of the College and their guests. The College lent many of its distinguished portraits and other articles of interest to the Philadelphia Museum of Art for the exhibit. All the Fellows were invited to attend and to bring guests with the purpose of acquainting more Philadelphians with one of its great old medical institutions, The College of Physicians of Philadelphia. A Women's Committee was formed under the able leadership of Mrs. George I. Blumstein to handle the innumerable details which had to be taken care of for such an occasion.

The reception proved to be a great success. Some 500 people attended and I am sure that you all have heard what a pleasant occasion it was. I am certain that none of this would have been possible without the hard work of the Women's Committee. We hope that the Women's Committee will continue to be active and work with the Officers and Council to keep the public aware of the activities of the College and to help arrange for lectures, television programs and other matters of interest to the general public.

The expenses of the reception amounted to $2,743 while the contributions totaled $3,540. Thus contributions from the Fellows amounted to approximately $800 more than the expenses.

W. B. Saunders Company agreed to furnish us without charge 1,000 copies of an illustrated brochure about the College, briefly recounting its past history and current functions. Following the reception, this brochure was mailed to everyone who attended. Within the brochure was a subscription blank for membership in the "Friends of The College of Physicians of Philadelphia." The form indicated that $10 was an annual subscription for an individual, $15 for a family, $25 for a contributor, $50 for a sponsor and $100 or more for a sustaining membership. As a result of this mailing, $800 was contributed by both Fellows and guests.

The Erlanger Garage

In my report to the Fellows last year, I made an error in stating that the College paid $142,000 for the Garage building and the property it stands on. There were other items in the cost which I was unaware of. The total cost of acquiring the property was $158,905. The property was purchased in 1957 principally to ensure that parking facilities adjacent to the College would always be available to the Fellows. Nine years later the wisdom of this action becomes abundantly clear. Plans are nearing completion for the construction of a building on the parking lot on the west side of 22nd Street across from the College building. When construction starts, the loss of the parking lot will be a serious inconvenience to Fellows using the Library or attending scientific meetings.

For two years, the Finance Committee and the Council have discussed and con-

sidered how to increase income from the property and reduce expenses. Throughout these discussions, it has been unanimously agreed that the College should not sell the property, as the reasons for the original purchase still obtain, i.e., to assure a parking area for the Fellows and/or room for expansion of the College. Land values are going up in the neighborhood and at the present time the property could undoubtedly be sold for at least $30,000 more than it could have been last year. Mr. Jack, our agent, renegotiated the lease for the garage on March 1, 1965, with the result that our tenant now pays us $900 per month. The tenant, I am happy to say, is currently up to date with his rent payments. Nevertheless, there are serious drawbacks to our continuing with the present arrangements because of costly repairs to the building which are urgently needed. The roof should be repaired at a cost of $3,500. The flooring on the street level should be replaced and our insurance carrier is presently requesting extensive repairs to the elevator. Our insurance costs, real estate taxes and water and sewer rent amount to well over $5,000 a year. With an extremely optimistic estimate of $2,000 in repairs to the building for the next year, the estimated return on our investment of $158,905 will be only 1.88 per cent.

If the building were demolished and the lot black-topped and leased as a parking facility, our taxes and insurance would be greatly reduced, there would be no repairs and the return on our total investment of $196,305 (a figure which includes the cost of demolition and paving) would be 2.5 per cent. Therefore the Council, at its November meeting, instructed Mr. Jack to give our tenant notice of our intention to discontinue the lease as of March 1, 1966. At its December meeting, the Council studied the figures reported by our Treasurer, which I have given above, and voted unanimously to proceed with demolition of the building and paving of the lot at the termination of the present lease. Whether the College will lease the lot for operation as a public parking area, or reserve it for use of the Fellows of the College, will have to be determined in the light of future events.

Finances

I am happy to report that for the first time in several years, we ended our last fiscal year in the black. Table I shows the cumulative deficit ( ) or excess of income over expenses at the end of the last four fiscal periods. Figures are given for the General Operating Funds, the Library Funds and for the College as a whole as a summation in the last column. If you will look at the last column first, you will note that there was a slight deficit at the end of the fiscal year on 10 November, 1962. On 10 November, 1963, the cumulative deficit was $26,000. It was at this point that the Council reluctantly voted to increase the annual dues of the Fellows. On June 30, 1964, after a short fiscal year of eight months, the cumulative deficit amounted to only $1,600. This figure, however, is not significant because almost $90,000 of dues had been received from the Fellows in the first six months of the year 1964. The bot-

TABLE I

Cumulative Deficit ( ) or Excess Cash Position

(to nearest $100.00)

Date Ending Fiscal Period	General Operating Funds	Library Funds	Total College
10 November 1962	(10,300)	10,100	(200)
10 November 1963	(38,500)	12,300	(26,200)
30 June 1964	(23,200)	22,800	(1,600)[1]
30 June 1965	(500)	5,300	4,800[2]
		+14,000[3]	+14,000[3]

[1] Dues increased 1 January 1964.

[2] $650,000 of securities sold and reinvested. Securities in Maintenance and Reserve Fund sold and $23,800 transferred to General Operating Funds.

[3] Library Special Account.

tom figure in the last column, I am happy to say, *is* significant. This represents an excess of income over expenditures during the fiscal year which ended on June 30, 1965. This figure does not include an additional $14,000 available in the Library Special Account, which is used for our journal acquisition program.

During all four fiscal periods shown, there was always a cumulative deficit in the General Operating Funds and a cumulative excess in the Library Funds. This occurred because of generous appropriations from the General Operating Funds to the Library Funds in each fiscal period recommended by the Finance Committee and approved by the Council. Finally, it should be pointed out that Table I is a greatly simplified version of the finances of the College. Nevertheless, the figures for the last fiscal period indicate correctly that the financial condition of the College has greatly improved.

The $23,800 transferred from the Maintenance and Reserve Fund to the General Operating Account is, of course, a nonrecurring item of income. Despite the sale of these securities, the total income-producing securities held by the College of Physicians increased in market value by $13,000 during the past fiscal year from $1,925,000 on June 30, 1964, to $1,938,000 on June 30, 1965. Other assets held by the College which produce income are, of course, the Erlanger Garage and the Joseph N. Pew, Jr., Memorial Loan Fund, from which the College receives for its operating account approximately $1,200 annually. The mortgage remaining on the property at 13th and Locust Streets at the end of our fiscal year amounted to $30,000. The money annually received for reduction of the principal of this mortgage is added to our General Endowment Fund. I am also happy to state that last week the Pew Foundation contributed an additional $25,000 to the Joseph N. Pew Memorial Loan Fund, increasing its total assets to approximately $60,000.

The S. Weir Mitchell Associates now number 130 and the work of the S. Weir Mitchell Committee continues under the able chairmanship of Dr. George I. Blumstein. As I stated last year, the formation of the S. Weir Mitchell Associates is the most significant fund-raising project in support of the library in the past few years.

Finally, I know you are all saddened, as I was, by the death of one of our distinguished Fellows, George W. Norris, who died December 1, 1965. In his will Dr. Norris left a life estate for his widow, Mrs. Norris, and directed the payment of $10,000 from the residuary estate to The College of Physicians for the maintenance of the Norris Room and Norris portraits. He also directed the transfer and delivery of the ultimate remainder of his estate to the College of Physicians of Philadelphia to be added to and become a part of the General Endowment Fund. It is understood that the likelihood is that this ultimate gift to the College will probably be well over a half million dollars. Bequests of this type are very heartening because they indicate devotion, interest and affection for this grand old institution.

Plans for the Future

Members of any institution in our society today must make plans to adapt the structure and organization of that institution to the inevitable and continually occurring changes in our social, economic and scientific environment. Currently we are faced with an enormously rapid growth in scientific knowledge and technology. Obviously these scientific and technological changes have a significant bearing on the operation of our Library and in the means of communication with our Fellows and the lay public. For example, the Philadelphia Regional Medical Library Committee have almost completed the draft of a grant re-

quest for Federal funds to initiate the transmission of textual material in the College library over existing telephone wires to the five medical schools in Philadelphia where the texts will be reproduced. This would constitute a great improvement over the use of the mails or other means to transport the requested material to the interested individual. The College should be the center for the Medlars program of the National Library of Medicine or any other method of retrieval of medical information which might prove to be superior. For communication and public relations, I am sure we should initiate series of lectures for the public or television programs on a monthly or more frequent basis. To consider these and other matters your President, with the approval of Council, is appointing a Planning Committee. This Special Committee will report its recommendations to Council.

Your Officers have for many years realized that, despite the time they devote to the interests of the College, many matters essential to the welfare of the College remain unaccomplished. I think the Officers and Council are unanimously agreed that for the College to grow and thrive and change, we must have a full-time, salaried Director. Therefore, one of the first tasks assigned to this Planning Committee will be to find such a Director. Our sister institution in New York, the New York Academy of Medicine, has long had a Medical Director and the New York Academy has, for many years, interested the public in their activities through public lectures, television programs, etc. I am sure that it would be impossible to arrange such programs without a Director. I personally believe that either a lay person or a physician could function admirably as the Director of our College, provided he or she were imaginative, interested and dedicated to the job.

Finally, I would like to thank the Officers, the Council, the Chairmen and Members of the Committees of the College and all the Fellows for their loyal and continued support during the past year. In addition, I would like to thank especially our Librarian, Mr. Elliott H. Morse, for his activities on behalf of the College during the past year, activities which extend far beyond the customary duties of a librarian. Our Executive Secretary, Miss Olga E. Lang, has continued her long and devoted service to the College and has earned the gratitude of all our Fellows. Mr. Theodore J. Kolodziejski, our Superintendent, continues to display initiative, imagination and industry in his job for which we are very grateful.

The Primate Socialization Motives[1]

By HARRY F. HARLOW, PH.D.[2]

THE various species of the Primate Order, which includes monkeys, apes, and men, have shown relatively direct, progressive capabilities of socialization throughout the course of evolutionary development, with the result that it is easy to conceptualize the human being as the most social animal ever to be created. However, it should be recognized that primates, both human and simian, are animals endowed with many motives more suited to individual survival than to group living. Such basic motives as hunger, thirst, fear, and rage elicit, or tend to elicit, responses of self-survival so that man and his next of kin are inherently a very different type of social animal from, for example, the social insects, which suffer little conflict between motives for personal survival and motives for social survival.

The primates' capacity for socialization stems from the fact that in addition to the individual motives of survival they also possess complex motives which endow them, both innately and through learning, with strong, positive feelings toward members of their social group. In all primates the self-survival motives and the social motives are often in conflict. In well-run monkey societies there are personal quarrels leading to psychic and physical pain and occasionally to injury and mayhem. In well-run human societies there are also individual or intragroup quarrels and conflicts, and these can have tragic consequences. Whether or not these conflicts and quarrels are more serious in groups of men or monkeys is an open question. However, primate social motives have triumphed over individual-survival motives in all existent simian societies so far.

We have broadly defined the socialization motives as the affectional systems and have presented the position that within, and probably even without, the primate order there are at least five affectional systems (7). These are: the mother-infant or maternal affectional system, the closely related and complementary infant-mother affectional system, the age-mate or peer affectional system, the heterosexual affectional system, and the paternal affectional system.

During the last several years we have directed our primary research emphasis toward the analysis of individual affectional systems, including the developmental or growth stages through which each progresses and the determination of the relative roles of the various stimulus variables, including the experiential, which elicit, regulate, and order them. The data obtained from a family of researches led us to the conclusion that in all probability the age-mate or peer affectional system, rather than the maternal affectional system, was the primary intraspecies socialization mechanism determining subsequent successful heterosexual adjustment and maternal behavior (6). This position is supported in a recent study by Alexander and Harlow (1) which showed that baby monkeys raised with cloth surrogate mothers while being denied any opportunity to interact with peers during the first six months of life had greater difficulty in making effective social adjustments during preadolescence and adolescence than did baby monkeys raised by adequate mothers, brutal mothers, or no mothers whatsoever but permitted ample opportunity to establish

[1] Alvarenga Lecture XXV, The College of Physicians of Philadelphia, 1 December 1965.

[2] Director, Primate Research Center, University of Wisconsin, Madison, Wisconsin.

affectional relationships with their agemates during the first half-year.

Although research techniques designed to analyze the individual affectional systems and to ascertain their relative importance throughout the total socialization process are justifiable and even meritorious, it is obvious that the various affectional systems do not operate independently and exclusively during the course of socialization in the primate animal. The various affectional systems must appear and elaborate in an orderly and integrated manner and in such sequences that the normal development of the early affectional patterns prepares the animal for the kind of social adjustment that will transpire as each of the subsequent affectional patterns appears.

Mother-Infant Affectional Relationships

By definition the primary affectional systems in terms of ontogenesis, if not of importance, are those of the interacting maternal affectional system and the reciprocal infant-mother affectional system. The initial stage of the mother-infant affectional interaction in the rhesus monkey transpires during the infant's first four or five months of life, and an analogous affectional stage persists in the human being for four to five times as long. During this early developmental stage, the normal monkey mother responds to her infant almost totally positively, giving it tender, loving care and punishing it only infrequently and then but mildly.

During the early stage of mother-infant interaction the normal mother effectively and efficiently carries out three primary functions: (a) she satisfies her infant's physiological requirements, including food and warmth, (b) she meets her infant's psychological needs of intimate bodily contact and comfort, and (c) she protects her infant from the animate and inanimate threats in the external environment. The protective function is very broad, including guarding the baby from predators or hostile monkeys, guiding the infant in the selection of appropriate and inappropriate responses to physical and social environmental stimuli, and comforting the infant when it is frightened or hurt. Thus the protective functions are, in fact, closely allied to the maternal bodily contact and comfort behaviors.

During this early stage of affectional development, the infant's responses to the mother are essentially reciprocal. The infant monkey's reflex clasping, clinging, and climbing responses aid and abet nutritional needs, since they position the baby ventrally on the mother's ventral surface and thereby insure oral nipple contact, one component of the infant monkey's maternal contactual pattern, illustrated in Fig. 1. The infant rhesus also shows a strong propensity toward imitation of maternal responses directed toward the external environment, a mechanism that facilitates early maternal guidance.

Fig. 1. Neonatal monkey showing oral and manual clasp pattern.

The human neonate is so physically immature that it cannot clasp, cling, and feed back to the mother as effectively as the neonatal monkey, but this does not mean that its early affectional requirements are basically different. The human neonate has the same contactual, nutritional, and protective needs as the monkey, but its immaturity places a heavier burden of responsibility upon the human mother and prolongs the period of dependency.

The product of this primordial mother-infant affectional interrelationship from the point of view of the infant's social development is the formation within the infant of strong feelings of safety and security in the physical presence of the maternal figure. All three of the described maternal functions doubtless play a role although our own researches on the surrogate mothers indicated that bodily contact with the mother superceded nursing and calmed the frightened animal. The development of infantile feelings of safety and security are essential since within this period the primate infant has itself matured to the point that strangeness has become a fear stimulus in and of itself, and the infant requires the maternal haven of protection if it is to operate effectively in adjusting to the outside world. Thus, the development in the infant of security and trust in its contact with the mother prepares it for the second stage of mother-infant affectional relationships.

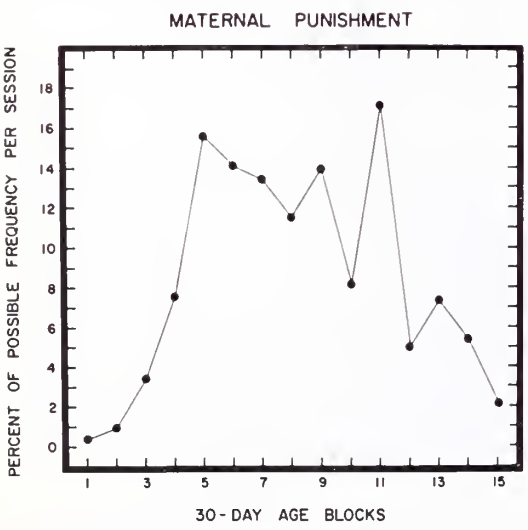

FIG. 2. Frequency of maternal punishing responses.

The second stage of mother-infant affectional relationships is one in which the infant gradually emancipates itself from the pervading need of physical maternal attachment, and if this stage is blocked either by infantile or maternal incapacity, the infant will be socially crippled. From the infant's point of view, the basic mechanisms of maternal emancipation are the strong motivations of curiosity and exploration which lead the infant to investigate the physical environment that surrounds it even though this of necessity means the temporary severance of maternal contact. Exploration of the physical world takes two forms: exploration of nearby physical objects and exploration of nearby animate objects, and the most important of these objects are other infants, preferably infants of similar ages.

It is our firm belief that maternal emancipation is not only achieved through the operation of the infant's curiosity and exploratory responses but that it is abetted by simultaneous changes in the mother's behavior which take the form of discouraging continuous bodily contact by mild rejection from time to time. We have described this second maternal stage as that of ambivalence or transition. Although the mother throughout this second stage exhibits strong protective functions whenever these are required, the physiological needs, particularly the nutritional needs, of the infant are gradually waning as other food sources become available and the compelling needs of intimate bodily contact and comfort are also declining or possibly merely being superceded by the incompatible needs for exploration and broadened social contacts. Thus, the effective primate mother in this second period is one which not only gradually accepts

infantile separation, but which even encourages it. During this second mother-infant developmental stage the normal monkey mother shows a decreasing tendency to restrain its infant's explorations and also an increasing frequency and severity of punishment responses directed against her infant (see Fig. 2) even though these responses are seldom, if ever, cruel or abusive. Whatever the mechanisms eliciting these maternal punishment responses may be, we strongly suspect that they serve a useful function in supporting the infant's own tendencies to emancipate itself.

The Age-Mate or Peer Affectional System

If the monkey infant achieves maternal independence and is afforded opportunity to interact with age-mates, the age-mate affectional system will inevitably develop. The primary mechanism producing these effective age-mate adjustments is that of physically interactive play, and social play between monkey infants goes through a threefold developmental process, progressing from rough-and-tumble play, to approach-withdrawal or noncontact play, and culminating in aggressive play. Rough-and-tumble play, illustrated in Fig. 3, is characterized by vigorous wrestling, rolling, and sham-biting responses which involve little or no physical discomfort. Noncontact play is characterized by back-and-forth chasing responses by two or more animals with actual physical contact being kept to a minimum. During the latter part of the first year of life the two patterns may become intermixed, and we have sometimes given this alternating and relatively violent pattern of play sequences the special name of interactive or mixed play.

Aggressive play, which develops shortly before or after the first year of life, is similar in form to rough-and-tumble play but the bouts are now characterized by aversive components. The manual contact and release may now be physically painful, and the biting responses may evoke cries of distress and anguish from the victim. Normal

Fig. 3. Rough-and-tumble play pattern.

rhesus infants are seldom injured during these aggressive play encounters, but firm peer relations establishing dominance position and social status develop both between and among the masculine and feminine infants. Thus we conceive of aggressive play as having an important, positive social role in which the monkeys learn through early experience to try, test, and accept the differential and changing status positions they will occupy during adolescence and adulthood.

Out of the early age-mate affectional interactions the monkey learns the techniques by which it expresses dominance when dominance is appropriate, and submission when submission is required. Thus early play experience trains the monkey to meet the ever increasingly complex patterns of social ordering in monkey societies composed not only of other age-mates, but also of adults, both male and female.

There is nothing mysterious about play behavior. If infant associates are available, play behavior invariably appears and follows a sequence almost as predictable as the developmental sequences of locomotion and prehension. Doubtless play does prepare the infant to assume later adult roles, but so also do locomotion and prehension, and there is no need to assume a teleological explanation. The play sequence is the complex resultant of the maturing of motor and intellectual abilities, the satisfaction of emerging and developing needs for activity and exploration, and, eventually, of the affectional ties that spring from and, in turn, become strengthened by the playful interactions.

Just as the maternal and infantile affectional patterns prepare the monkey infant for entrance into the stage of peer attachment, so does the age-mate affectional system prepare the older infant or juvenile for entering successfully into the complex social requirements of the heterosexual, maternal, and paternal affectional systems.

The Heterosexual Affectional System

The heterosexual affectional system has a long ontogenetic developmental history starting with reflex pelvic thrusting in the neonatal period to any soft, warm surface, such as the mother's body, and progressing in infancy to differential sex behaviors commonly characterized in the male by threatening and following behaviors, and in the female by passivity and rigidity responses. Thus, from early infancy onward there is a tendency, when playful physical interactions take place between male and female, for these interactions to be broken off by the female, which in turn retreats and assumes either a passive or rigid body posture with head averted, and a tendency for the male to follow and make physical contact. These physical interactions by their basic nature lead the male to achieve dorsoventral contact with the female, and probably through some learned process which has not been adequately analyzed, male and female infants show ever increasing frequency of play behaviors which mimic the adult-type male and female sexual postures basic to normal adult heterosexual interactions. However, normal adult heterosexuality involves more than the formation of appropriate postures and motor skills. Both males and females must be willing to accept physical contact by age-mates if normal adult heterosexuality is to be accomplished, and we believe that the acceptance of physical contact is also achieved through age-mate play behaviors. Furthermore, normal heterosexual behavior cannot be attained if the aggressive responses which mature from the second year of life onward are not ameliorated and modulated by the earlier intraspecies affectional responses which also develop out of the early stages of interactive play. Just as the normal operation of the maternal affectional system in association with the normal development of the infant-mother

affectional system prepares the organism for age-mate or peer affectional relationships, so do the complicated interactions involved in the age-mate or peer affectional system prepare the monkeys, both male and female, for the adolescent and adult expressions of normal heterosexual behavior.

The Maternal Affectional System

Maternal behavior is in turn based on a family of early-experience variables. At least from late infancy onward the female monkeys show far more interest in baby monkeys then do equal-aged males, and this female interest expresses itself as if the female had a specific need to make positive contactual responses to young monkeys. Thus, before motherhood is normally achieved the female monkey is a highly baby-oriented animal predisposed to welcome or initiate intimate contactuality with infants and, through this contactuality, achieve the complete pattern of normal maternal responses. The same factors that predispose the female to be contactually responsive may also be responsible for the greater frequency of grooming behavior engaged in by females as contrasted with males.

However, we have a wealth of data which show that any innate maternal propensities are not adequate in and of themselves to endow the rhesus mother with normal maternal capabilities. In those cases in which we have impregnated by dark and devious means, female monkeys which had been denied opportunity to form age-mate affectional relationships during the first year of life we have produced mother monsters which were either indifferent to their newborn infants or cruel, brutal, and even lethal. Thus it is obvious that early age-mate association is as essential to the fruition of the later maternal affectional system as it is to the heterosexual affectional system.

We are convinced that the playful interactions which characterize the development of the age-mate affectional system are the basic mechanisms through which monkeys, and probably people, develop generalized feelings of affection for other members of their species. Monkey mothers that have been denied age-mate affection treat their infants with no more concern than they would treat inanimate objects, and those mothers which are aggressive vent their aggression against their own babies in a manner totally devoid of any restraint.

Paternal Affectional System

Laboratory and field studies, particularly field studies, clearly demonstrate that the mature adult male is a highly social animal protecting all members of his group or clan and showing particularly intense protective responses toward young infants, even to the point of occasionally adopting infants for a considerable period of time when these infants have become separated from their mothers, probably because of the advent of a second baby or the death of a mother. Little or nothing is known of the variables, innate or acquired, which lead the adult monkey male to assume these protective functions, although the phenomenon has been demonstrated time and time again. It is, however, inconceivable to us that an adult male monkey would ever adopt an effective paternal role if he had not gone through the peer affectional stage. Indeed, males raised in social isolation for the first or second six months of life subsequently, as adolescents, show aggression toward younger monkeys in contrast with the friendly behavior of socially raised males of the same age (5).

Effects of Social Isolation

A basic method which we have used to analyze the variables underlying the development of the affectional systems is that of social isolation, in which monkeys are

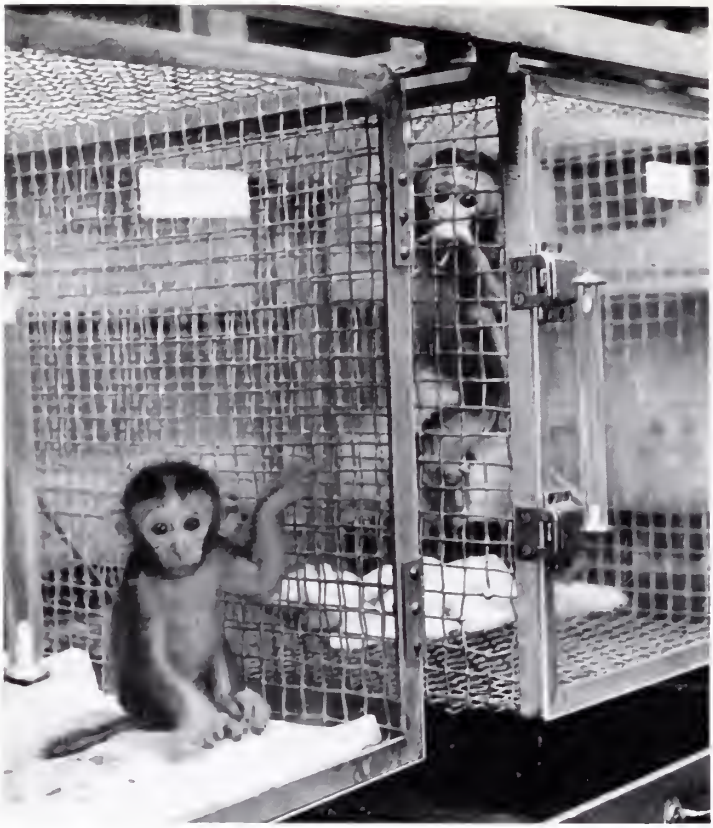

FIG. 4. Partial social isolation cage.

denied any opportunity to form affectional relationships with any other member of their species for predetermined periods of time. We have described one of our isolation techniques as partial social isolation, and it is achieved by raising monkey from birth onward in individual wire cages, as illustrated in Fig. 4, in which the isolates can see and hear other monkeys but cannot make any physical contact with them. This technique makes it impossible for the infants to form any mother-child relationships, and it also makes it impossible for them to form adequate age-mate or peer affectional patterns because any opportunity for interactive play is excluded.

We have raised groups of rhesus monkeys under partial social isolation for periods ranging from a few months to more than 7 years and have traced the development of abnormal personal behaviors which appear under this condition (2). Early in life there is a high incidence of diffuse disturbance patterns which include nonnutritional orality, self-clutching, and convulsive jerking. An extreme form of the self-clutching pattern is illustrated in Fig. 5, and we have referred to it as an autistic pattern of response, recognizing that the human autistic pattern is more complex and more variable. These behaviors tend to decrease with time as the animal matures and/or adjusts to its restricted environment, but other dramatic abnormal patterns take their place. One of these is repetitive stereotyped movements, such as repetitively pacing back and forth across or around the cage, or circling compulsively from the top to bottom of the cage, and these abnormal individual patterns

FIG. 5. Autistic disturbance pattern.

are more persisting than those of nonnutritional sucking or autistic posturing. A third dramatic abnormal pattern which we have observed is one to which we have given the name "catatonic contracture," and it may appear within the first two years of partial social isolation. While the monkey sits in a quiescent state, often staring blankly into space, an arm slowly and gradually floats upward with concurrent flexion of the wrist and fingers—a movement made as if the limb were not an integral part of the monkey's own body.

As long as monkeys are maintained in our partial social isolation situation we see no increase in fear responses, probably because the animal learns that in the cage it is safe from the threats of animals in adjacent cages. However, we know that animals so raised exhibit intense fear of each other or of more normally raised agemates if they are placed in a social test situation with them after enduring six months or more of partial social isolation. Thus, though we do not see the development of social fears as long as the animal is maintained in the partial isolation situation, these social fear responses are ready to be manifested outside the home cage.

The phenomena relating to the development of aggression are much more striking. The developmental trends may be measured by the simple technique of observing the animal while one experimenter slowly runs his hand, covered by a large black laboratory glove, over the subject's cage. This black glove is familiar to all the laboratory monkeys since it is used by handlers for protection when making direct contact with the animals. Two patterns of aggression are displayed and show progressive increase in frequency under this condition. One pattern is aggression directed toward the observer, and, as is shown in Fig. 6, this behavior attains near maximal frequency in the second year of life for the male and by the fifth year of life for the female. The second pattern is that of aggression by the animal against its own body, characterized by biting its own hand, arm, foot, or leg. As is shown in Fig. 7, this pattern has a relatively high level of frequency by the fourth year of life in the male and by the sixth year of life in the female. Sex differences in the development of the aggressive patterns are interesting in that aggression is one of the few behavioral patterns to mature earlier in the male than in the female.

We now have a large body of data on the effects of partial social isolation on the animal's subsequent ability to adjust so-

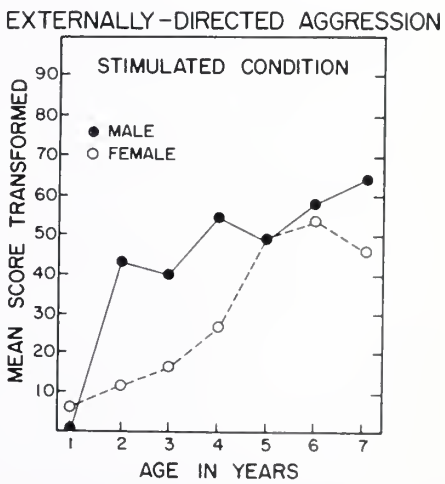

FIG. 6. Development of externally oriented aggression.

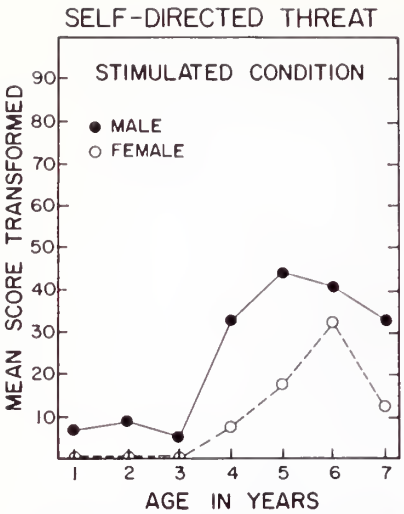

FIG. 7. Development of self-directed aggression.

cially to age-mates. Prolonged partial social isolation progressively depresses any capability of social interaction, probably heightens aggression or perhaps only appears to because it prevents learning of restraints in expressing aggression, and inhibits or destroys heterosexual interaction and maternal capabilities. Actually partial social isolation is almost as socially destructive as total social isolation, but in the following pages we will limit our presentation to the effect of early, complete social isolation because of our greater abundance of long-term total isolation test data.

Total social isolation was achieved by raising various groups of rhesus monkeys in a stainless-steel chamber illustrated in Fig. 8 from a few hours after birth until 3, 6, or 12 months of age. In addition, one group of monkeys was raised for the first six months in individual cages in the nursery, then subjected to total social isolation for six months. During the period of confinement the monkeys had no social contact with any animal whatsoever. Sensory deprivation was held to a minimum since the chamber was constantly illuminated, transmitted sounds, and afforded limited opportunities for cutaneous-proprioceptive expression and exploration.

The effects of total social isolation were appraised by comparing the interactions of social isolates with the interactions of control animals exposed to our playroom situation illustrated in Fig. 9 (see Harlow, Dodsworth, and Harlow [5]) as stable groups of four composed of two isolates

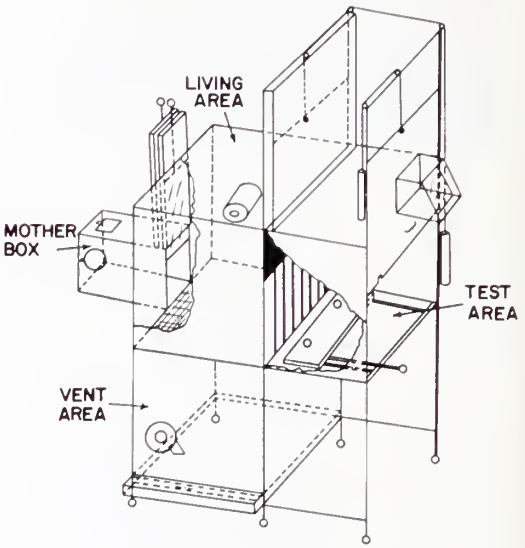

FIG. 8. Total social isolation chamber.

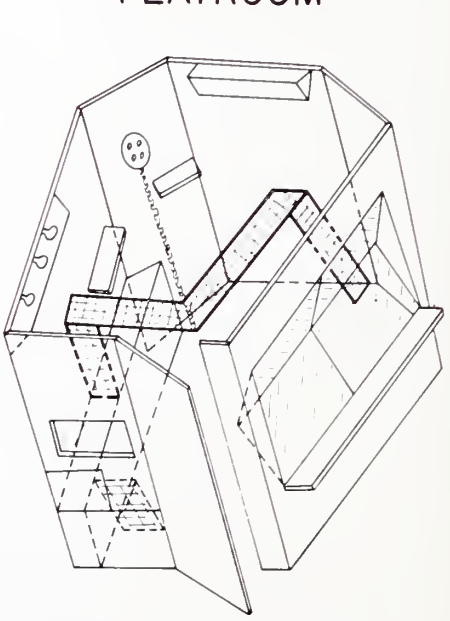

FIG. 9. Playroom situation.

and two control animals. In each instance the controls were not normally raised animals but monkeys of the same age raised in partial social isolation. Macaque monkeys raised in total isolation for 3 months are terrified when they are released from the isolation chamber and placed in standard laboratory cages. However, when the period of initial shock subsides, the 3-month total social isolate monkeys make a surprisingly good adjustment to the control age-mates, and as is shown in Fig. 10, we see no indication of any differential frequency in social threats in the members of the experimental and control groups and find no differential incidence that is statistically significant in the frequency of contact play in the isolate and control groups. Thus, rhesus monkeys show a rather surprising capacity to recover from this relatively brief period of total social isolation although we are by no means convinced that there are not some long-term residual effects, at least in some of these subjects.

A far different picture, one of social devastation, is found in the case of macaque monkeys which have undergone 6 or 12 months of total social isolation and have

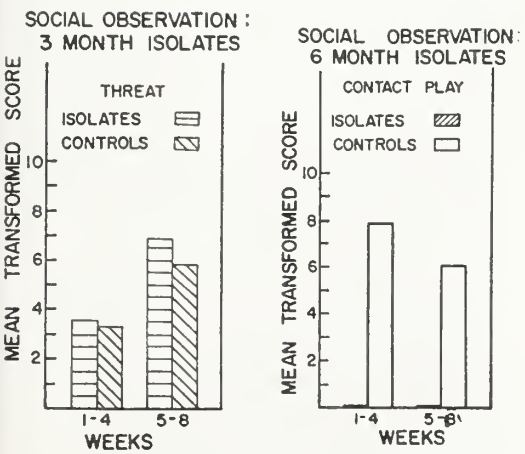

Fig. 10. Effect of three months' total social isolation on incidence of social threat.

Fig. 11. Effect of six months' total social isolation on contact play.

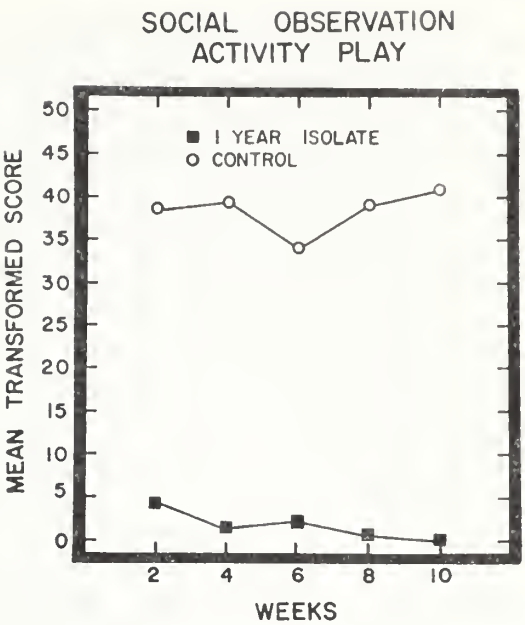

Fig. 12. Activity play in 12-month isolates.

then been tested with pairs of control age-mates in the social playroom. As is indicated in Fig. 11, contact play is high in the control animals and almost nonexistent in the 6-month isolate animals. The slight increase in play which the isolate monkeys show from 24 weeks onward is limited entirely to play with each other; the isolate monkeys have never exhibited any form of positive social interaction with the controls. The controls themselves are retarded in social interactions as compared with monkeys given social experience with peers from at least 3 months of age onward.

Although 6 months of total social isolation obviously resulted in drastic curtailment of social activity, the monkeys subjected to 12 months of isolation were even less active. As is shown in Fig. 12, even activity play—self-play not involving social interaction—is essentially nonexistent in the 12-month isolates, and these 12-month isolate monkeys are the only animals we have ever seen in which autoerotic sex behavior was almost nonexistent. As Fig. 12 shows, the experiment was concluded at the

end of 10 weeks. This action was taken because the year-old controls were exhibiting progressively greater violent aggression against the totally helpless isolate monkeys, and we were convinced that the isolate monkeys would have been killed had we continued testing for a longer period of time. Probably a more socialized control group would have been less aggressive toward the isolates but none was available. There were also two pairs of animals isolated between 6 and 12 months of age. Upon release and exposure to the social playroom one pair was markedly hyperaggressive and abused the control animals, and the other pair held its own with the controls but was not ascendant.

These combined data strongly suggest that rhesus monkeys can recover from a limited period of social isolation beyond which there results a progressive social incapacitation until a point is achieved from which there is probably no recovery. If we interpret our data in terms of a critical period or critical stage hypothesis, it would appear that the first three months of life is not the critical period or the most critical period for the development of socialization in these animals. However, the following three months represents a very critical stage, and in all probability every succeeding month is progressively more devastating and, at least statistically speaking, dramatically lowers any possibility of social rehabilitation until the likelihood of social rehabilitation becomes for practical purposes nonexistent. Not surprising is the qualitatively different effect of total isolation coming after an early period of only limited restriction. Although no human infant could survive the kind of total isolation to which the monkeys were subjected, human infants are sometimes reared under conditions of partial social isolation in institutions. The data suggest that they may suffer damage in the last quarter of their first year of life but may recover if removed. After 12 months in an unstimulating institution the probability for recovery decreases, and after 24 months, the human being raised under social restrictions is a very poor risk for future adjustment in a normal environment.

Mechanisms of Socialization

Psychologists, anthropologists, and sociologists have placed great emphasis on the importance of learning in the development of socialization. No one will deny the importance of social learning or deny that learning variables play progressively greater roles as primate social organizations become progressively more complex. However, the fixation on the role of learning by many socially minded theorists obscures the fact that success or failure of primate social learning is dependent upon many basic, complex, unlearned behaviors that progressively mature long after birth. In rhesus monkeys masculine and feminine behaviors are relatively undifferentiated during the first 90 days of life but are progressively more differentiated thereafter, and learning is in no sense the variable of primary importance. Maternal behavior changes during the periods of gestation and parturition and the sequential development of primate play patterns are not to be explained by learning alone. However, above and beyond the maturation of these relatively specific social behaviors the natural and orderly sequential development of three major categories of behavior determines in large part the success or failure of primate socialization.

Affection, Fear, and Aggression

In all primate species, in all mammalian species, and in many or most vertebrate species there is an orderly development of affection, regardless of the specific form it takes, of fear, and of aggression. One or more forms of affection precede the appearance of specific environmental fears, and fear in turn precedes the development of intraspecies aggression. Thus in the

macaque monkey intense mother-infant affectional responses are formed in the first days of the infant's life and have become deep and enduring during the first month. Fear of strange external stimuli, even though they may be of low physical intensity, are first evident between 60 to 90 days of age, and as we have already indicated, intraspecies aggressive responses play no important social role until the macaque monkey is approximately one year old.

In the human being infant-mother affectional ties are established during the first half-year of life, fear of strangeness, characterized by Spitz as eight-months' anxiety, typically develops in the second half-year of life, and aggression between human children attains social importance between the third and fourth year.

Puppies form warm relationships to their mothers during the first few hours or days of life, show fear of unfamiliar objects by the sixth or seventh week (3), and develop intraspecies aggressive responses at some later period of time.

Below the class of mammals are the data on many species of nidifugous birds. The imprinting process which we will include as an avian infant-mother affectional mechanism normally develops at birth or shortly thereafter. Fear of external stimuli develops after the sensitive period of imprinting, and if imprinting is not achieved before these external fears develop, the very process of imprinting may be difficult or impossible (see Spalding [9], Hess [8], and Fabricius [4]). The development of social aggressive responses has not been traced in birds, but it clearly follows the appearance of fear and is definitely present in the courtship and mating patterns. In those fish which lack parental ties, the first positive bonds would be with peers. Fear must appear early if the fry are to survive at all, but aggression presumably appears much later. For guppies we have a few informal observations that support the principle of delayed appearance of aggression for this species. Guppies removed from a tank with adults soon after birth very quickly show no avoidance of peers. Placed with larger but immature guppies, they avoid the larger fish. Three- to four-month-old guppies approaching maturity do not attack two-week-old guppies, but mature guppies immediately attack two-week-old guppies and even incapacitated mature guppies.

Social isolation is a technique making it possible to eliminate all opportunities for affectional formation until fear of external stimuli or of strangeness and until socially aggressive responses have developed. Fear of strangeness appears in monkeys by 90 days of age, and all rhesus monkeys subjected to total social isolation for three months or more show intense fear to strange environmental stimuli, animate or inanimate. Indeed, this period of panic may be so extreme as to be lethal. Our own data indicate that this fear of strangeness becomes more pervasive and prolonged the greater the period of social isolation, but this may be an artifact of our test situation. The older our isolated monkeys are when they are introduced into the playroom with pairs of strangers, the older and more aggressive are the strangers, and the progressively increasing fear of the isolates may consequently be the result of being confronted by more and more ominous social stimuli and more and more abuse.

Macaque monkeys subjected to total social isolation for the first year of life show no aggressive tendencies when paired in the playroom with control age-mates. We attribute this to the fact that their aggressive tendencies are hidden by their overwhelming social terror. Two of the monkeys subjected to total social isolation during the second half-year of life, contrariwise, turned out to be extremely hyperaggressive, and the other two were a match for the controls. We assume that while they had no opportunity to form affectional attachments in their first six months, they

did have a chance to adjust to fear of strange situations, including other monkeys, leaving delayed aggression to flourish without tempering by affectional attachments after their release from isolation and introduction to social stimuli.

We also have long-term follow-up data on the monkeys subjected to total social isolation for both the early social isolates (first six months of life) and the late social isolates (second six months of life). When these monkeys were approaching or had reached adolescence they were subjected to social tests with stranger adults, stranger age-mates, and one-year-old juveniles. Theoretically by this time aggression has had ample opportunity to reach or approach its maturational peak.

Most of the monkeys in both the early and late social isolation groups exhibited violent aggressive tendencies of strange, bizarre, and socially maladaptive types. Frequently the social isolates would engage in a single act of aggression against a stranger adult, a suicidal act that no socially experienced adolescent would ever attempt. In all cases social learning was rapid. Furthermore, the social isolates, both male and female, would frequently aggress against defenseless young juveniles, a social transgression not seen in normal adolescent monkeys.

The developmental sequence of the emotional trilogy of affection, fear, and aggression provides a basis for primate socialization and doubtless for the socialization of many other species. The early affectional bonds between mother and child and the subsequent peer affectional bonds provide basic social security before external fear can arise. Members of one's own species, particularly one's own social group, are external objects which do not induce terror, indeed, they become security-providing objects. If, however, no opportunity has been afforded for the formation of affectional alliances with members of one's own species until after fear of strangers has developed, the capability of subsequent socialization will be seriously impaired.

If affection for members of one's social group has developed through normal mother-infant relationships and normal peer relationships before full-fledged aggression has matured, the later expression of aggression toward in-group members will be greatly ameliorated, and the full force of aggression can be turned against external enemies and predators instead of in-group associates. Failure to develop in-group affection before aggression is fully matured leaves the animal a deviate, a delinquent, and a social outcast. Both the self-survival motives of fear and aggression become effective social forces if they operate within useful social bonds, but if they operate against useful social alliances they convert the individual into a scapegoat on the one hand or a social menace on the other that cannot and will not be tolerated by his society.

Acknowledgments

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Virus-Induced Synthesis of Enzymes[1]

By SEYMOUR S. COHEN, PH.D.[2]

IT is a great privilege to have the opportunity to join the group of medical scientists who have previously presented the Hatfield Lecture. Many of the important researches in medicine recorded in these lectures have had a decidedly chemical bent, and a biochemist, without medical training, need not feel out of place as a lecturer. When Dr. Hatfield was a student in the early 1820s attending courses at the University of Pennsylvania and at the Jefferson Medical College, the role of chemistry in the medical curriculum was considered by many physicians to be relatively unimportant. Indeed in 1818 at the School of Medicine at the University of Pennsylvania, the right of the Professor of Chemistry to sign diplomas of its graduates had just been rescinded. As a result of such a decision a famous chemist, then teaching chemistry and geology at the University, was moved to write a long and increasingly famous document to the Trustees of the University protesting this deprecation of the role of chemistry in medicine. This detailed statement, entitled "A Discourse on the Connection between Chemistry and Medicine", may well be the first published survey of the state of biochemistry in the English language. The author, Thomas Cooper, had been the friend and assistant to Joseph Priestley, a Judge in Pennsylvania and a Professor of Chemistry and Natural History, as well as an active participant in the cultural life of Philadelphia. He had also been given an honorary degree in medicine. At the conclusion of his protest to the Trustees, Cooper summarized his position by saying that "Chemistry, as it applies to Medicine, is as in the infancy of Hercules".

Despite this defense of the role of chemistry in the medical curriculum, a passing grade in chemistry, affirmed by a Professor of Chemistry in the School of Medicine, was not required in this city for some years after Dr. Hatfield was given his diploma. However, it is clear that the list of Hatfield Lecturers and the subjects of their interests and efforts indicates a considerable change in the attitude of Philadelphia medicine on this question in more recent times. It may be noted that at the exhibit of "The Art of Philadelphia Medicine", which took place this past year, a portrait of Thomas Cooper painted by Charles Willson Peale was displayed, on loan from the collection of this College of Physicians.

Introduction to Biochemical Virology

My subject relates to the chemistry of virus-infected cells. This is a very recent specialization founded on many earlier basic discoveries. Neither Benjamin Rush or Thomas Cooper knew of the existence of viruses, although virus diseases such as yellow fever plagued Philadelphia and occupied the thoughts of our early physicians. Some of these diseases were ascribed to newly discovered "noxious airs", and it is interesting to see that in this respect medicine has not changed too much in 150 years, although we have more good reason today to be suspicious of the atmosphere we breathe. The great discoveries of Jenner and Pasteur on the virus diseases of smallpox and rabies certainly came within Dr. Hatfield's purview as President of the City Board of Health, although viruses as such were not actually discovered until a decade after his death. That these parasites were a

[1] Nathan Lewis Hatfield Lecture L, The College of Physicians of Philadelphia, 5 January 1966.

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proper subject of chemical study was not clear until 1931, when Schlesinger purified a bacteriophage and Stanley crystallized tobacco mosaic virus. Viruses were discovered to have nucleic acid in 1936 when Schlesinger demonstrated DNA in the bacteriophage he had purified and Bawden and Pirie detected RNA in plant viruses.

The next decade saw many studies on the isolation and characterization in chemical and physical terms of many kinds of virus particles. In this period these studies were also extended to the animal viruses, and the possibility of developing various killed vaccines from purified virus suspensions was pursued very actively under the impetus of World War II. I was working with Stanley on properties of purified plant viruses when this country entered the war, and I left to begin work on the purification of rickettsial and rickettsial antigens for purposes of improving the typhus vaccine. Indeed, I came to the University of Pennsylvania in 1943 in pursuance of that aim. Stanley also shifted the work of his laboratory at that time to the preparation of a killed influenza virus vaccine, whose preparation and characteristics are essentially the same as some of the influenza vaccines widely used today.

The work on virus purification and characterization not only gave important impetus to the development of vaccines, but also has provided many clues to the nature of virus multiplication. For example, it soon became clear that viruses lacked important constituents commonly found in and essential to all cells capable of growth and multiplication. These missing components, as noted fairly early, included the enzymes associated with energy production, e.g. cytochromes, tricarboxylic acid cycle, etc. The list is now known to extend to enzymes essential to the production of low molecular metabolites, such as amino acids and nucleotides, as well as to polymerases capable of synthesizing proteins and nucleic acids. These deficiencies alone may be supposed to define the dependence of a virus upon the enzymes and metabolism of the host cell in which it multiplies, i.e. the parasitism which the virus displays in the course of its multiplication in an infected cell.

All viruses were also revealed to contain nucleic acid. Unlike all multiplying cells which contain both DNA and RNA, viruses contain only one or the other nucleic acid as their genetic elements. Although the multiplication of all cell parts appears to be based on DNA as the key genetic element as far as we know, many viruses contain only RNA as their genetic element. Virus multiplication, therefore, can involve new types of genetic systems. Although my early work was on plant viruses and on influenza virus, which are RNA viruses, our work on virus multiplication has involved mainly a group of DNA viruses. The Rickettsiae, on which I had worked throughout the War, have proved to have both DNA and RNA, detectable energy generating systems, and a morphology and reproductive cycle much like the Gram-negative bacteria. For these reasons the Rickettsiae are now considered to be bacteria rather than viruses.

Throughout the early work on purified virus preparations it appeared to me that biochemical studies in virology had excluded the most potentially exciting opportunities in this area, i.e. the exploration of biochemical events during the multiplication of the viruses. Such an exploration could not occur in an intact plant or animal; indeed the confusion in the literature created by individuals who had tried just this is still quite unresolved. I tried to explore, in 1945 in the laboratory of Dr. Dale Coman, the suitability of tissue cultures for such a "simplified" virology, but lacked the patience that that apparent witchcraft seemed to require. In 1946 Dr. Coman was able to demonstrate in a technique and conception very advanced for the time that rabbit papilloma virus induced prolifera-

tion in cultures of epithelial cells (1). This important, indeed basic, finding has had to wait almost twenty years for its confirmation.

In any case, the needs of an impatient biochemist possessed of limited laboratory resources required a very much more convenient virus system. Dr. Thomas Anderson explained to me that bacteria infected by bacterial viruses could provide such a system, being amenable to quantitative assay, ready isolation of purified virus and facile manipulation of large masses of infected host cells. Furthermore a number of unusual investigators, including M. Delbruck, S. Luria and A. Hershey as well as Anderson, were exploring the biology and physics of the system and would welcome the biochemical information I might contribute. Thus reassured by the elegance, simplicity and rigor of the experimental system, I began our first studies in the biochemistry of virus-infected cells, in general, and of T-even phage-infected *E. coli* in particular.

From Discovery to Problem

When I began to look at infected bacteria in 1945, it was evident that I was all alone in an almost uncharted biochemical universe. At that time the nutrition, intermediary metabolism and the definition of the enzymes of cells were assuming central positions in the development of biochemistry. Of all of the possible facets one might explore, I ought to select one or more critical to the economy of virus multiplication. Which ones were these? I elected to look at what was then a relatively esoteric and unexplored area, the nucleic acids and their interrelations with protein synthesis, because these substances, i.e. the nucleic acids and proteins, were present in the viruses. This approach may seem obvious today but until comparatively recently most chemically oriented investigators studied the energy metabolism of infected cells because information on this area and an appropriate methodology were available and not because energy metabolism had any promise for the study of virus multiplication. With great delight we soon found ourselves overwhelmed with observations of peculiar phenomena in nucleic acid and protein syntheses in infected cells, presenting innumerable problems to be explored. Although most scientific papers are written in such a manner as to suggest that the authors were trying to solve clearly defined problems, our initial studies were carried out in an attempt to scan our system and to define the potentially significant problems. In the past decade this biological system, whose chemical parameters we began to sketch, has become one of the most important tools in dissecting the details and nuances of gene action in terms of the determination of protein synthesis by the nucleic acids.

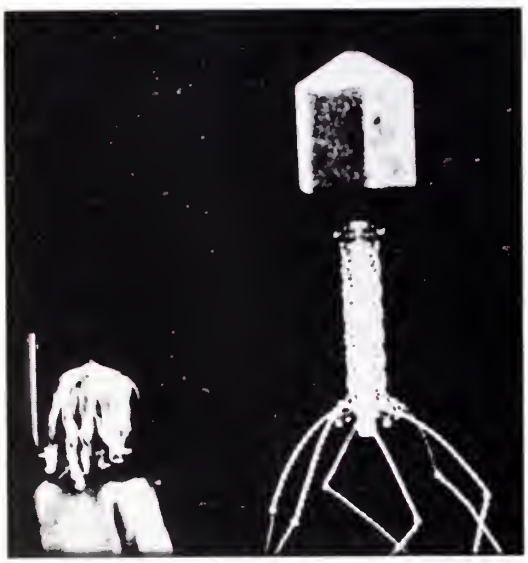

Fig. 1. A model of a T-even bacteriophage (at left). Courtesy of Seattle World's Fair.

A model of one of the group of viruses with which we have been concerned for two decades is presented in Figure 1. The viral chromosome consists of DNA and various cations and is encased in protein units comprising the hexagonal head. The tail of the virus is covered by a hollow contractile sheath containing both ATP and an ATPase, as well as activating Ca^{++}

ions. At the distal end of the sheath can be found a hexagonal plate to which six tail fibers are attached. These fibers make contact with a bacterial receptor, and the virus settles or is pulled to the bacterial surface. Lysozyme on the phage tail helps to open up the bacterial wall as a result of enzymatic degradation. Contraction of the sheath releases a spike within the tail core, penetrating the cell wall and opening the central tube for passage of the viral DNA into the bacterium.

In one of our first experiments we observed an unusual pattern of polymer synthesis in infected bacteria as compared to normal growing cells. In the latter, protein, RNA and DNA increased in a balanced fashion, doubling as the cells doubled, with the ratio of RNA to DNA maintained at about five. In infection, as shown in Figure 2, protein synthesis continued at a constant rate, determined by the numbers of protein-synthesizing factories, i.e. the ribosomes, existing when virus was added. When the virus inserts its DNA into the infected bacterium, the cell loses its ability to make its own structural proteins and enzymes, including ribosomes, i.e. loses its ability to double itself.

The inability of the infected bacterium to accumulate RNA also defines part of the inability of the cell to make the RNA-rich ribosomes. The problem of how infection effects this remarkable switch-off of host synthesis, first detected in 1946 (2, 3), remains a mystery. This phenomenon is not general and occurs only with a few bacteriophages; in terms of the development of chemical virology we have been fortunate to have explored this system first, since the existence of only the extreme alternatives of synthesis of cell substance or of virus substance have helped to simplify our problems.

Nevertheless, a small amount of RNA is made throughout infection, as detected by P^{32} incorporation into the RNA fraction (4). This RNA has a composition resembling virus DNA rather than host DNA or

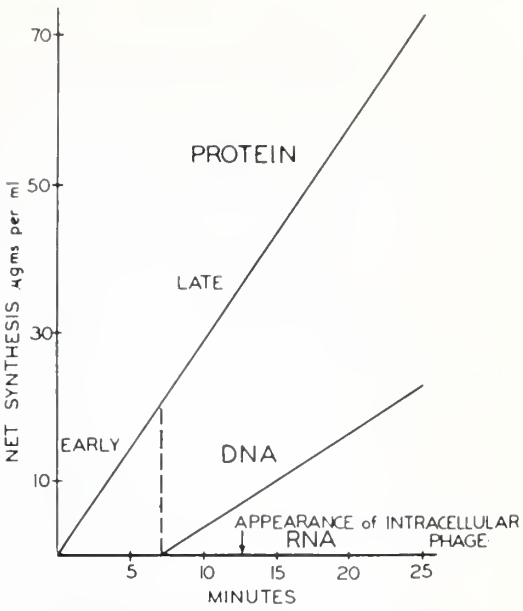

FIG. 2. The synthesis of proteins and nucleic acids after T-even phage infection (3). In contrast to uninfected cells, proteins are synthesized at a constant rate (3). RNA does not accumulate and its synthesis is detectable only by isotopic methods (4), and synthesis of viral DNA requires prior production of early proteins (3).

RNA, and has a rapid turnover. Indeed, this was the first discovery of messenger RNA, defined as an RNA made on DNA, which determines the quality and course of protein synthesis on ribosomes. As we shall see, such RNA indeed determines the production of the proteins that appear during infection.

It can be seen in Figure 2 that DNA synthesis begins relatively late, indeed after the initial formation of the unusual virus-induced RNA and the synthesis of some early proteins. The DNA made after infection is entirely viral DNA (3). Inhibition of early protein synthesis by amino acid analogues prevents synthesis of viral DNA (3); more recently we demonstrated that prevention of the first RNA synthesis also prevents synthesis of early proteins (5). The gross aspects of the control of synthesis of viral protein synthesis can then be described by the following sequence:

Viral DNA $\xrightarrow{\text{transcription}}$ Virus-induced RNA

$\xrightarrow[\text{Host ribosomes}]{\text{translation}}$ Virus-induced proteins

However it was shown that proteins made before DNA synthesis were not virus structural proteins (6), although these "early" proteins were essential for production of viral DNA. On the other hand, proteins made after production of viral DNA were predominantly virus structural proteins. Our problems were now defined and one of these will be the main subject of my lecture:

1. What are the virus-induced early proteins? For the most part, I shall discuss their origin and role in phage multiplication as well as their possible general significance.

2. What determines the control of production of the two different classes of protein, i.e. early proteins essential for production of viral nucleic acid, and late proteins or the structural proteins of the virus? How is the switch from the production of early proteins to that of late proteins effected within the curve of apparently unbroken protein synthesis? The problem of the nature of the switch or switches is key here, since the constant rate of protein synthesis throughout both phases is merely a function of the invariant number of ribosomes blindly grinding out protein in response to the messenger RNA supplied.

The Nature of Some Early Proteins

Until 1952, we used to say that a virus merely changed the direction of the existing polymer-synthesizing apparatus. In that year however it became possible to suppose that viruses might also expand the metabolic machinery, and indeed this supposition now appears to be generally true for most if not all virus infections. This generalization can be suggested ten years after a most singular initial discovery made with these unusually virulent viruses. This discovery was the detection, characterization and synthesis of a new and virus-unique pyrimidine, found only in the T-even phages and related viruses (7). The new compound was 5-hydroxymethyl cytosine, replacing the cytosine which is found in bacterial DNA and RNA. This new pyrimidine is built into a deoxyribonucleotide in the usual way but within viral DNA the hydroxymethyl group is glucosylated to different extents and in different ways. Although the glucose residues do not appear to contribute to genetic determination, their distributions are genetically determined. Their presence on the DNA does protect viral DNA in the infected cell against nucleases which eventually degrade the host DNA and can readily degrade nonglucosylated viral DNA. Having found this pyrimidine, we wanted to know its metabolic origins, to define the enzyme which made the compound, and to understand how this enzyme made its appearance.

It was shown that the pyrimidine ring is generated in the usual way via orotic acid and uridylic acid (8, 9). Furthermore bacterial deoxycytidylate would serve as a precursor (8) whereas various hydroxymethyl pyrimidines or their nucleosides were not precursors of either of the viral pyrimidines, 5-hydroxymethyl cytosine or thymine (10). The ability to make both pyrimidines was generated by virus infection of a bacterium normally unable to make thymine (11). This study had revealed for the first time that virus infection could confer new metabolic capabilities. In addition we discovered the phenomenon of thymineless death as a byproduct of defining the biology of the system (11). As many of you may know, thymineless death appears to determine the lethality of anti-tumor agents such as fluorouracil, fluorodeoxyuridine (12) and amethopterin.

When it had been demonstrated that neither the new pyrimidine nor thymine could be synthesized at the metabolic level of the free pyrimidines or as nucleosides, it became evident that we had to work with

cell-free extracts to study nucleotide reactions. Nucleotides cannot penetrate these bacteria (13). At about this time an enzymatic route for thymidylate synthesis (14) had been demonstrated in cell-free extracts of uninfected *E. coli*, as presented in Figure 3. We were able to show that extracts of infected cells contained about five times more of this enzyme (15). Furthermore, although extracts of thymineless bacteria lacked this thymidylate synthetase, extracts of the infected previously thymineless bacteria contained large amount of this enzyme. Such a virus-induced enzyme is now known to be different from the normal bacterial enzyme and indeed the nature of this enzyme differs according to the virus used in the infection, as determined by inhibition with fluorodeoxyuridylate (16).

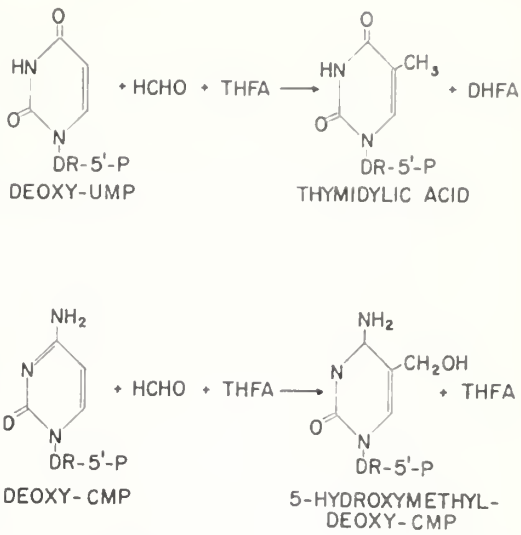

FIG. 3. Enzymatic reactions for synthesis of viral pyrimidines.

As for the new viral pyrimidine, hydroxymethyl cytosine, an enzyme, deoxycytidylate hydroxymethylase, present only in T-even virus-infected cells will add formaldehyde to deoxycytidylate in the presence of tetrahydrofolate to generate the virus-specific deoxyribonucleotide (15, 17). An uninfected bacterium does not contain even one active molecule of this enzyme (18). The new enzyme has a molecular weight of about 64,000 (19) and has been isolated essentially free of bacterial protein (2).

The Origin of a Virus-Induced Enzyme

We demonstrated that protein synthesis was essential to the appearance of the hydroxymethylase (21) and of the synthetase (22). This result complemented the observations that these enzymes were not injected by the virus, nor were they inhibited in the uninfected cell. Nevertheless, a requirement for protein synthesis does not prove that the proteins synthesized are actually the enzymes themselves. For example there might be a bacterial protein precursor which is activated by removal of a polypeptide via a newly synthesized proteinase. This activation could be analogous to the conversion of trypsinogen to trypsin. Another possibility is that a polypeptide precursor might be activated by addition of a small peptide.

Having learned how to isolate the hydroxymethylase in a pure state, after about five years of effort, we were able to test these possibilities. The enzyme contained considerable methionine. Methionine-requiring bacteria were grown in the presence of C^{14}-methionine, labeling the bacterial proteins very extensively. We permitted the bacteria to exhaust the methionine from the medium and to stop growing. Growth began again, after addition of nonradioactive methionine, and after replacement of the internal radioactive pool by unlabeled amino acid the cells were infected by virus for twenty minutes. Purified enzyme was then isolated and shown to be completely devoid of radioactivity (20). Thus this viral-induced enzyme was shown not to have a preexisting bacterial precursor and to be synthesized completely after infection from an exogenous supply of amino acids according to information supplied by viral DNA.

Although the other proteins which appear in viral multiplications seem to be comparable to the hydroxymethylase with respect to an origin de novo, it is not entirely certain that certain apparently virus-induced enzymes generated in animal and plant systems will have such an unequivocally de novo and virus-determined origin.

In our studies we have detected five such early proteins, i.e. three others in addition to the deoxycytidylate hydroxymethylase and the thymidylate synthetase. These include a deoxycytidylate deaminase (17), a dihydrofolate reductase that can operate with DPNH instead of TPNH (23), and ribonucleotide reductase (24). Other laboratories, such as those of Kornberg, Greenberg, Buchanan, Bessman, Levine, etc. have demonstrated at least ten other early enzymes and proteins in T-even phage infection (25). New enzymes concerned with DNA synthesis are being discovered in this system almost each month. The limit of the number of proteins coded for in the viral chromosome is 100 or more, for which the geneticists have detected about 50 genetic sites with over 40 relating to late functions. Such late functions include production of at least seven virus structural proteins, and other as yet undefined functions important to virus maturation and release. It is evident therefore that this system will provide a well stocked fishing pool for biochemists and geneticists for many years, if not for many generations.

On the Generality of Virus-Induced Enzymes

Early enzymes and proteins including nucleases, kinases, DNA polymerases, thymidylate synthetases, etc. have been found in other phage-infected cells. The role of these enzymes, as in T5 infection, appears to assist in expanding DNA synthesis. However, in other systems, such as T3 infection, an enzyme is generated which destroys S-adenosyl methionine; the role of such an enzyme produced only in this system is obscure at this time. In lysogenic systems the production of a nuclease appears important, although obscurely so in its exact significance, in converting the system from lysogeny to vegetative virus multiplication. In systems infected with animal viruses containing DNA, e.g. vaccinia, herpes simplex, thymidine kinase and other enzymes such as thymidylate kinase, nucleases, and DNA polymerase are very frequently observed to increase greatly in amount, although the significance of such increases is not clear.

Even in infection with DNA tumor viruses, novel enzymes and proteins have been detected, e.g. arginase in papillomas produced by Shope papilloma virus and the ubiquitous nuclear neoantigens or T antigens produced early after infection with polyoma virus or SV40 virus. The phenomenon therefore extends to these instances also and although its significance is as yet quite obscure, the possibilities are compelling widespread study.

With RNA viruses, such as RNA phages, plant viruses, or certain animal viruses, e.g. polio, Mengo, encephalomyocarditis, etc., the production of viral RNA appears to require the production of new and specific virus-induced RNA polymerases. The properties of such polymerases are being investigated in many laboratories at present. On the other hand influenza virus stimulates the production of neuraminidase, of unknown import, and this phenomenon has been virtually neglected. Numerous murine leukemia viruses appear to be associated with lactic dehydrogenase, although it is not known if this enzyme is produced as a result of infection.

Clearly then, the appearance of early enzymes and proteins is widespread in virus infection and the nature of the proteins involved vary according to the nature of the virus and the often unknown

exigencies of virus multiplication. A vast Pandora's box has been opened and the emerging problems will both plague and nourish virology for many years.

On the Possibilities of a Specific and Selective Chemotherapy

What might be the practical interest of the phenomenon of virus-induced enzymes? Among the most obvious is the consequence that a virus-infected cell will have significant differences in its metabolic machinery from that in an uninfected cell. There will be one or more new enzymes in such infected cells and it may be imagined, on paper at least, that this new array of amino acids, possesses new configurations in secondary, tertiary, and quaternary structure which will be uniquely sensitive to a well designed inhibitor. If this unique sensitivity is really so, and such an inhibitor can be inserted in active form into infected cells, and the process controlled by the new enzyme indeed contributes to virus multiplication, the possibility exists for a selective and specific chemotherapy of certain stages of virus disease. This possibility may be suggested to extend even to some phases of tumor development involving tumor virus infection and multiplication.

Are scientists bright enough and industrious enough to take advantage of such a possibility in animals and man? I suspect that this is most unlikely. The requirements for such an enterprise, including the investment in the cooperative activity of capable chemists and biologists is so considerable that there is little likelihood that such a coordinated venture will be mounted deliberately. However, it is quite possible that prepared minds will stumble on useful compounds which take advantage of the phenomenon of virus-induced enzymes. Ineed in a recent significant breakthrough in viral chemotherapy, the use of 5-iododeoxyuridine in the treatment of herpetic keratis in rabbits and man, it appears that the potential value of virus-induced enzymes may have actually been exploited.

It has been known for many years that numerous compounds can jam virus multiplication in tissue cultures but fail to do so in the intact animal. The compounds frequently are unable to survive body defenses and attain a suitable concentration at the site of infection. The experimental ophthalmologist, Kaufman, recognized that an infection of corneal cells by herpes simplex virus approaches the apparent simplicity of an infected tissue culture, at least with respect to treatment with an inhibitor; Kaufman (26) discovered that the thymidine analogue, IUDR, which blocks multiplication of herpes virus in tissue cultures, will also do so when applied frequently in eye drops to an infected eye. The compound has a very low toxicity for normal cells, thereby approaching the goal of specific chemotherapy.

As noted above, infection with herpes virus or vaccinia virus appears to stimulate production of thymidine kinase in infected cells. This enzyme can phosphorylate both thymidine and IUDR with ATP, as presented in Figure 4. Normal corneal cells have a very low level of this enzyme, in-

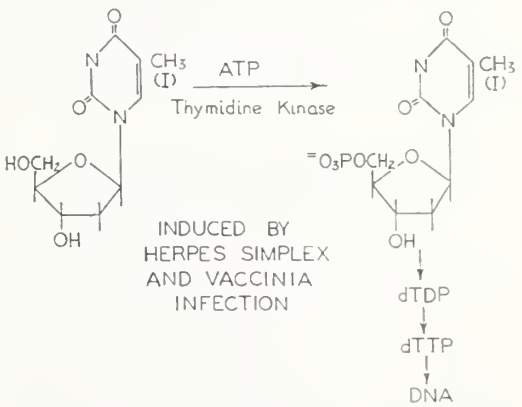

Fig. 4. The role of virus-induced thymidine kinase in the activation of the antiviral chemotherapeutic agent, iododeoxyuridine (IUDR).

corporating very little thymidine or IUDR into cellular DNA. Infected cells, as a result of the increased level of thymidine kinase, will incorporate relatively great amounts of these nucleosides into viral DNA. Both phosphorylated thymidine or IUDR can be converted to the respective nucleoside triphosphates which are substrates for DNA polymerase. However viral DNA that has incorporated iododeoxyuridylate instead of thymidine appears to be incapable of organizing normal viral particles, and virus multiplication is markedly inhibited.

In tissue cultures it has been possible to isolate virus strains resistant to IUDR and such strains are unable to generate thymidine kinase (27). It is not yet clear if the IUDR-resistant strains which frequently emerge in treatment of human herpetic keratitis are similarly deficient in thymidine kinase. However the possible role of this enzyme is posed most sharply when it can be seen that viruses lacking the required genetic component can multiply readily. However it appears in the case of vaccinia virus at least, that IUDR-resistant strains are less pathogenic than wild type strains for rabbit skin, but not for human amnion cells (28). In any case the multiplication of such IUDR-resistant strains of herpes virus or vaccinia virus is inhibited by other therapeutically interesting compounds, such as D-arabinosyl cytosine, which act by a different mechanism.

On the Control of Synthesis of Virus-Induced Proteins

I have discussed at length some aspects of the relation of the presence of new viral genes to the formation of the end products, the virus-induced proteins. Although I would very much like to discuss the problem of the nature of intermediate steps, I do not have time to do more than summarize some of our work and thoughts in this area. It has been clear that the RNA synthesized after infection determines the nature of the proteins made but very little is known of the properties of such RNA.

Two types of hypotheses can be imagined to account for the observed sequential appearance of early and late proteins after insertion of the total viral genome into the bacterium. The problem is formally analogous to the sequential appearance of proteins and structures during embryogenesis. These hypotheses are:

1. All types of RNA serving as message for synthesis of viral-induced proteins are made immediately. RNA for early proteins are selected preferentially by the ribosomes. These RNA molecules are used, degraded preferentially and are eventually replaced by the more stable RNA active for synthesis of late proteins.

2. Virus DNA is transcribed sequentially into different classes of RNA, i.e. messenger RNA for early proteins is made early and RNA for late proteins cannot be transcribed. The synthesis of early RNA is stopped by DNA synthesis. After this, RNA for late proteins is made.

Following the discovery of the distinctive virus-induced RNA by Volkin and Astrachan (4), we have studied the degradation in cell-free extracts of such RNA made relatively early in infection. It has been shown that this RNA is associated mainly with ribosomes, presumably for use as messages in protein synthesis, and we have described its degradation by two bacterial enzymes, i.e. to ribonucleoside diphosphates by polynucleotide phosphorylase, and to ribonucleoside 5′-monophosphates by a phosphodiesterase (29). These ribonucleotides can then be converted very rapidly in the extracts to deoxyribonucleotides and incorporated into DNA (30). However these metabolic processes do not seem to be well suited to the fine controls required for the sequential appearance of the different proteins.

To test these hypotheses, we have used

some unusual bacterial strains which after infection can make characteristic virus-induced RNA without protein synthesis (31). At least three quarters of such RNA become attached to the bacterial ribosomes, which are charged and ready to make early enzymes. When these infected bacteria are given the essential amino acids they respond with a burst of synthesis of early proteins which is switched off shortly after DNA synthesis begins. Until DNA synthesis begins, the production of late proteins cannot be detected and we have concluded that the viral DNA is transcribed initially to yield only the RNA for early proteins. We think this supports the second group of hypotheses.

If DNA synthesis is blocked by infection with ultraviolet-irradiated virus, the cell not only makes early proteins but continues their production abnormally without ever making late proteins. We have interpreted this to mean that the separation of DNA strands essential for DNA synthesis is the molecular switch that turns off synthesis of RNA for early protein (31). Further, it appears that the DNA synthesized in infection may be essential to the production of RNA for late proteins; such a hypothesis is also supported by genetic evidence (32).

It should be clear that we have not delved as deeply as we would like into the problems of control described in this lecture. A start has been made however and the results only lead us to ask additional questions, such as: What prevents the early synthesis of RNA for late proteins? How are the DNA strands separated, i.e. how is the switch thrown? Is RNA for early proteins made late and if so, why isn't such RNA used?

Conclusion

In short, our work has only led us to additional problems, many of which we do not yet know how to approach experimentally. However, I trust I have been able to indicate to you that the questions with which we are now confronted in infected *E. coli* are of the most general significance in virology and in understanding mechanisms of development generally. The recognition of the broad interconnectedness of biological phenomena can not but help assure future experimentation on these questions, with the continuing enlightened interest and support of our medical colleagues.

Acknowledgment

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The University in the Forefront of Community Action[1]

By WILLIAM A. STEIGER, M.D.[2]

TRADITIONALLY, Universities have *not* been in the forefront of action. *Action* has not been considered part of a University's role. The Cardinal Newman type of University concerns itself with ideas—not with action—with principles, knowledge, analyses, conceptions—in order to preserve old knowledge and to transmit it and to develop new knowledge therefrom. The University has dealt with the abstract—not with the concrete, in the main. The political scientist was not a politician; the historian did not fight the battles. To be active entailed the danger of the loss of objectivity. In medical schools, patients were necessary but only to practice on, learn from and implement research. The goal was education, not service, primarily. This viewpoint led, for example, to what has been recently tagged as "The Interesting Case Syndrome".

Now the situation is beginning to change in some Universities, especially it seems to me, in large, urban Universities, in what Clark Kerr has called Multiversities. What are some of the forces propelling this change—this change from scholarly isolation to active participation? One factor certainly is the Urban Sprawl, the increasing "slumminess" of the areas surrounding some metropolitan Universities. It has become increasingly difficult for such Universities to overlook the growing social problems which surround them.

Although not a MARXIST, I appreciate that economic determinants also enter as a factor in the change. Falling property values, increasing property destruction, large numbers of sick but impoverished patients, and finally Federal fund stimulation to *do* something—these are economic forces, negative and positive, that promote action.

Finally, underpinning much of our social activity, both within and without Universities is the philosophy of existentialism, especially French existentialism and Sartrian existentialism. Out of existentialism and incidentally out of the French Resistance in World War II, two words have developed deeper meaning, more profound connotations and heightened significance. These words are "commitment" and "engagement". To live passively under the tyranny of the Nazi occupation was to exist without essence, to *be* without meaning. To be committed to overthrowing the tyranny and to be engaged actively in so doing was dangerous to being but was the essence of living. It showed a concern for man, for humankind that was real and not abstract.

To return to the University, isn't it likely that the attitudes and especially the behavior of the University faculty has a more permanent and telling influence on the students than the facts of knowledge or the "poop", as I crudely put it? If scholarly isolation, if lack of engagement are the hallmarks of University preference and prominence, will not many of the graduates carry these values through life along with their parchment diploma? Martin Buber[1]

[1] Read before the 7th Regional Health Conference, Pennsylvania Department of Health, 5 October 1965. Joint meeting at the Lankenau Hospital with the Section on Public Health, Preventive and Industrial Medicine, The College of Physicians of Philadelphia.

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Selected Indicators—Morbidity and Mortality	City Health Districts				
	#10	#5	#6	#8	Nicetown-Tioga comparison (1961)
Tuberculosis/100,000 (Active + Potentially Active)	17.8	114.3	98.8	33.5	117.2
Syphilis/100,000	14.9	430.7	242.4	88.7	
Without Adequate Prenatal Care/1000	2.7	35.7	28.6	12.5	
Infant Mortality Rate/1000	15.4	40.7	37.2	26.4	54.9
Neonatal Death Rate/1000	12.7	27.3	23.3	19.9	43.7
Immature Births (%)	6.4	17.3	13.7	10.6	12.5

FIG. 1. Public Health Data: Health Districts of North Philadelphia (1963).

has said, "Knowledge (I believe he means abstract knowledge—book learning, so to speak) is an autopsy upon the corpse of 'real living' encounter or meeting in the present".

To Temple University, encounter or engagement means the establishment of a Center for Community Studies, training *Vista* volunteers for action programs, leadership of and participation in the Philadelphia Council for Community Advancement, with all the consequent difficulties and criticisms—often a price one must pay for taking action. It has meant using medical students in a skid-row health survey and the establishment of a treatment center there. It means State affiliation, in order to lower tuition costs and thus provide greater educational opportunity for a wider segment of our population.

To the Health Sciences Center of the University it means the establishment of some community for which it cares and takes care. This is being done in a cooperative effort between the Department of Health of the City, with Drs. Norman Ingraham and Walter Lear and their staff, and the staff of a new Department of Community Medicine. It entails the integration of human services, to which end the Community Nursing Service and the social and welfare agencies of our community have been meeting to participate in the planning effort. It means cooperation between Dr. Lewis Polk and the City Maternal and Infant Care Program and Temple's Department of Obstetrics-Gynecology. Boundaries between specialties have to be broken down, so that biological medicine, psychological medicine and social medicine can meet in actual encounter.

Being engaged in caring for a community requires understanding of the community and vice versa. (Figure 1). Engagement means provision of high quality, comprehensive, continuous, personal care, not undignified ward or clinic care, not anonymous care—but with freedom for any individual to opt for other care—or for no care in some instances. We are not Gods or Czars, but we are experts. We must reach out with the carrot, not with the stick!

Scholarly studies and surveys, such as the 600 neighborhood families interviewed this past summer by 6 of our medical students —are necessary—for this permits the actions taken to be intelligent, informed and rational. If we *only* study and survey and take no action except to write or read a paper, such as this one, might our students think that papers and meetings such as these are the ends to be cherished?

Jean-Paul Sartre[2] said of this: "Quietism is the attitude of people who say, 'let others do what I cannot do'." The doctrine I am presenting before you is precisely the opposite of this, since it declares that there is no reality except in action. It goes further, indeed, and adds, "Man is nothing else but what he purposes, he exists only in so far as he realizes himself; he is therefore nothing else but the sum of his actions, nothing else but what his life is." Hence we can well understand why some people are horrified by our teachings. On this point Sartre adds that many have but one resource to sustain them in their misery,

and that is to think, "Circumstances have been against me, I was worthy to be something much better than I have been. I admit I have never had a great love or a great friendship, but that is because I never met a man or a woman who were worthy of it. If I have not written any good books, it is because I have not the leisure to do so; or, if I have had no children to whom I could devote myself, it is because I did not find the man I could have lived with. So there remains within me a wide range of abilities, inclinations and potentialities, unused but perfectly viable, which endow me with a worthiness that could never be inferred from the mere history of my actions." But in reality and for the existentialist, there is no love apart from the deeds of love; no potentiality of love other than that which is manifested in loving; there is no genius other than that which is expressed in the works of art. Sartre states, "The genius of Marcel Proust is the totality of the works of Proust; the genius of Jean Racine is the series of his tragedies, outside of which there is nothing. Why should we attribute to Racine the capacity to write yet another tragedy when that is precisely what he did not write? In life, a man commits himself, draws his own portrait and there is nothing but that portrait."

Hopefully the portrait that will be painted of the Temple University Health Sciences Center will be one with a significant segment of faculty and students engaged in quality community care, its practice and study. Let me close with some quotes from President Millard Gladfelter of Temple University.[3] "First, we are an urban university. This is a planned fact, not a coincidence. When an opportunity arose for us to move out of the city and into the suburbs, we renewed our obligation to those who depend upon an urban center of learning by staying where we are and growing with our community. Our Broad Street location places us on the very spine of Philadelphia. Here, we can best serve those who need us most. The true essence of a university can best be measured by its value to society and the way in which it fulfills its obligation to be the center of the civilizing process. We at Temple University believe that the milestones of each year—those particular events which involve us with the community and the community with us—are paramount factors in achieving this essence."

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David Hayes Agnew, M.D. (1818–1892)[1]

By SAMUEL X RADBILL, M.D.[2]

WHEN I received this invitation to speak about Dr. David Hayes Agnew I was most agreeably excited. My conscience had been bothering me because some time ago I had been asked to write a biographical sketch of him as one of America's great medical educators, but was prevented by other commitments at that time. My loyalty to my *Alma Mater*, Penn, and my interest in the Philadelphia medical story, however, kept alive a desire to study his life and the times in which he accomplished so much. I am grateful for this opportunity to make amends for a previous lapse.

Dr. Dorothy Lansing has described me as a medical history "buff". Derived from the buff overcoats enthusiastic volunteer firefighters used to wear, the word buff came to be used for any kind of enthusiast. One of my earliest ventures as a medical history buff was over thirty years ago when I talked to my fellow ex-residents at the Lancaster General Hospital about the Pennsylvania Dutch Pioneer in American medical education, John Eberle, a native of Lancaster.

The year 1965 marks the bicentennial of medical education in the United States. I will therefore try to emphasize facets of the history of medical education in the life of D. Hayes Agnew. The Medical School of the University of Pennsylvania became the mother of medical schools in this country, and Chester County has been the birthplace of many prominent doctors. Thomas Ruston, who published an important essay on small pox in London in 1767, was born here; and from New Garden Township came Samuel Jackson, the first president of the Philadelphia County Medical Society.

D. Hayes Agnew had many ties with Chester County. He married Margaret C. Irwin and went into the iron business here with her brothers; after it was evident that he was not cut out for a business career, he then settled down to practice medicine at Cochranville in this county. He also had close affiliations with Lancaster County, where he was born in Christiana, at that time called Nobleville, in the pleasant Noble homestead which is now occupied by our colleague, Dr. Herbert L. Tindall, Jr. His father, Dr. Robert Agnew, a busy practitioner prominent in church work, was popular among his neighbors and served in the state legislature. His mother, Agnes Noble, was the daughter of an elder

FIGURE 1

[1] Read before the Chester County Medical Society and the Lancaster County Medical Society for the Bicentennial of Medical Education in the United States, 17 November 1965.

[2] Past Chairman, Section on Medical History, The College of Physicians of Philadelphia. Address: 7043 Elmwood Avenue, Philadelphia, Pennsylvania 19142.

of the church and the grandaughter of one of the founders of the original seat of Presbyterianism in America at Octorara (now Oxford, Pennsylvania). His mother and his grandfather instilled him with religious fervor that endured throughout his life. Like Ambroise Paré, Agnew never operated without first praying for divine guidance. His father built a flouring mill on the branch of the Octorara Creek at Christiana in 1816 and for many years the driveway leading over the embankment of the mill pond was a local landmark. D. Hayes Agnew had a very complete family record which his niece used after his death to prepare a comprehensive family account.

Dr. D. Hayes Agnew was one of the organizers of the Lancaster County Medical Society. In fact, this was the first medical society of the many to which he belonged. He was among the twenty-three who met on Valentine's Day, 1844, in a building on the Corner of North Queen and Orange Streets to organize the Lancaster City and County Medical Society. Forty-five years later he and Dr. Ehler were the last two survivors of this pioneer group. Among the many organizations of which he served as president were The College of Physicians of Philadelphia, the American Surgical Association, the Philadelphia Academy of Surgery, the Philadelphia County Medical Society and the Pennsylvania State Medical Society. The origin of the Medical Society of the State of Pennsylvania dates back to 1848, a year after the American Medical Association was founded, when the pre-existing societies of Chester, Philadelphia and Lancaster counties elected delegates to a state convention which met in Lancaster on April 11. The first thing adopted was the A.M.A. Code of Ethics, because this was the binding force of the profession. Dr. Wilmer Worthington of Chester County was the one man most influential in the establishment and success of our state society. He was noted not only for his professional attainments, but also for his executive abilities in professional, educational and commercial organization. One of the founders of the Chester County Medical Society in 1828, he was president of the state society in 1850.

Agnew received his early education at the Moscow Academy under Mr. Latta and his higher education at Jefferson College at Canonsburg, and later at Delaware College in Newark. He then studied medicine for a time at home under his father's tutelage. Apprenticeship to a practicing physician was still in vogue at that time. In 1836 he entered the Medical School of the University of Pennsylvania. He was now all of eighteen. His medical teachers were Chapman, Hare, Gibson, Horner, Jackson, Wood and Hodge, and his roster included courses in medical science, surgery, chemistry, materia medica and pharmacy, anatomy, midwifery and the institutes of medicine. Most of the teaching consisted of didactic lectures, although Professor Hare was proud of his fine chemistry laboratory where he not only demonstrated chemical experiments before the whole class but had laboratory cubicles where students could experiment for themselves. From the commencement of medical teaching in Philadelphia practical instruction was available. There were private schools of anatomy with demonstrations of surgical operations on the cadaver and dissection by the instructor and by the students themselves, and bedside instruction was given at the Philadelphia Almshouse and at the Pennsylvania Hospital. Students crowded around the bed while the professor examined and lectured about the patient. Those on the outer fringe of the crowd often could not see the patient or even, at times hear what the professor had to say, so that they would hasten to the next bed hoping to have a place close to the patient and the professor when he got there. Dr. Benjamin H. Coates had al-

ready introduced in 1834 the practice at the Pennsylvania Hospital of bringing the patient into a clinical amphitheatre, and when Gerhard and Pennock returned from their graduate studies in Paris around 1833 they, too, taught clinical medicine at the Philadelphia Hospital and at the Pennsylvania Hospital much as is done to-day. Surgery was also taught in these hospitals and Agnew could witness operative procedures and listen to the discourses of Gibson, Pancoast, Horner, Harlan, Hewson, Barton, Harris, Randolph and Norris, a corps of skillful surgeons from both schools of Philadelphia who attracted students from everywhere. A fee of ten dollars at each hospital entitled the student to see and hear all.

When Agnew entered the medical school student life was undergoing a transition, becoming more serious and sedate. In the past the medical students had been notorious for their boisterous, unruly conduct. Drinking and revelling with a gruesome sense of humor, they often offended the community wherever there were medical schools. London's *Punch*, with biting satire, lampooned them severely in a series of articles published in a book called *The Medical Student*, that had some influence in reforming their conduct. Youngsters coming from the country as freshmen often "wore a decidedly bucolic aspect in manner and apparel." Many of them came to Philadelphia from wealthy Virginia plantations and brought with them not only money, which they lavishly squandered, but rowdy conduct as well which led to medical students in general being called "Ginny students." They were feared especially by the colored people who foolishly believed these gay young doctors "burked" negroes to obtain bodies for the anatomical rooms. There was growing turmoil, also, about the question of slavery and states rights and the Southern students resented bitterly the increasing abolitionist activities in Philadelphia. Some students drank and wenched and so frequently fell into the toils of the police. One of the common duties of the medical professors was to bail them out of jail in the morning. Students and professors were much closer in those days. Almost every professor had a large class of private and office students in addition to his regular lecture classes. There was a long period from May to October between the regular courses. Two courses were required for graduation. To fill the gap between terms private schools were available: one of the early and popular ones was the Medical Institute established by Dr. Nathaniel Chapman. A native of Virginia, he became the acknowledged leader of the medical profession of the country in his time. Private quiz classes were also conducted. The first one was organized by Dr. Thomas D. Mütter, who later became professor of surgery at Jefferson Medical College.

Agnew graduated in 1838, before he was twenty-one. Like his predecessor William Darlington from Chester County, he frowned upon the frivolity of medical students and in his graduation thesis preached to them on medical ethics, the title of his thesis being: Medical Science and Responsibility of Medical Character. Returning to Nobleville he set up in practice. He had plenty of time for his favorite sport, hunting. His principle competitor was Nathaniel Sample, who was more mature, having been born in York County in 1780, and was trusted by the people. (Many, many years ago an ancient Hindu medical teacher, Susruta, enjoined his young students to raise beards because no one trusts a young doctor. Aesculapius was a veterinarian, a hippiatrist entrusted only with the care of horses, before he grew a venerable beard; and the baldpated Hippocrates was likewise full-bearded.) So the youthful tyro had plenty of time to ride to neighboring Pleasant Garden across the county line in Chester County to shoot game and woo the modest

maid he married in 1841. His father having moved to Maryland the year before, Agnew then went into business at their foundry at Pleasant Garden Forge on the old telegraph road between West Grove and New London. Living nearby, he was a member of the New London Brass Band. After three years, he returned to practice in Cochranville, a few miles south of Parkesburg. Here his competitor was a Dr. Windall. This may have been Lewis Windle who married Sallie Baker by a Friend's ceremony on June 8, 1859, and died in 1880.

An energetic young physician with time on his hands and an ambition to become a useful surgeon, Agnew began to dissect corpses which he obtained from Philadelphia. To clean the bones he placed them in a pond where the eels saved him this slow and bothersome job. Unfortunately there happened to be a local fisherman in the neighborhood who became famous for the fat and juicy eels he had to sell. Rival fishermen trailed him and discovered his choice fishing spot, discovering at the same time how the eels thrived so well! When the story spread, the people of the community were appalled. The climax came when someone fished up a skull with a hole in it. Agnew was suspected of obtaining his cadavers by shooting the victims through the head. He had a tough time explaining that the hole was just from practice with a surgical trephine on an inanimate skull. Even so, patients were less than enthusiastic about using a doctor who did not already know all there was to be known about medicine, and so in 1848 he moved to Philadelphia. That summer he substituted for the younger Dr. Sample in Soudersburg when Sample was sick, but his special talents were not meant for practice without teaching and research.

Agnew was not the only one in Chester County with the urge to dissect. Nearly two thousand years ago, Galen tried to learn anatomy by dissecting animals, but accurate knowledge about the human body can only come from study of human bodies. The Chester County Medical Society, meeting in the Hall of the Chester County Cabinet of Natural Sciences, pledged "to use every endeavor to overcome the existing prejudice against post-mortem examinations, and to embrace every opportunity for making such an acquaintance with morbid anatomy". William Darlington was the first president of this society and Wilmer Worthington its first secretary, both men highly respected in this community and of great repute. During the cholera epidemic in Philadelphia one broiling summer night, Agnew, in search of anatomical material, went to a pit in which unclaimed bodies had been dumped and injected as many as fifteen at one time in order to procure and preserve them for dissecting material. He was not above a trip to Potter's Field at midnight to resurrect a body, inject it for preservation, place it in a sack on the seat of his buggy alongside of him and drive to his dissecting school on Chant Street in Philadelphia.

How else was he to train the doctors who were so urgently needed to heal the sick? When The College of Physicians of Philadelphia, in 1867, was called upon to aid in the passage of a state anatomical law, long advocated by Dr. William S. Forbes, Professor of Anatomy at Jefferson Medical College, Agnew was appointed with Samuel D. Gross to serve on the committee with Forbes. They were the great surgeons of their day and highly respected. When they testified before the state legislature on behalf of Forbes' bill it was passed.

Agnew purchased the private Philadelphia School of Anatomy in 1852 when it was in a state of decline because of the illness of its owner, Dr. Allen. At last he had found an outlet for his real talent, teaching. He toiled incessantly, spending as much as twelve to eighteen hours a day

in the dissecting room. Every year, from September to March, he lectured there five evenings a week, and from August to April, three evenings a week. The dissecting rooms were open to the students for dissection from eight in the morning until ten at night. Gross, Levis, Garretson, Keen and others were demonstrators for him. All benefited from the practical training in anatomy there that led to success in surgery. When he took over the school, he had nine students; when he transferred his teaching activities to Penn, ten years later, his class numbered 267—the largest ever assembled in this country. In 1854 he established the Philadelphia School of Operative Surgery on the upper floors where he conducted separate classes, demonstrating on the cadavers all the known operative procedures. Students flocked to him from Penn, Jeff and the Philadelphia Dental College which had been recently started. Woman's Medical College and Hahnemann Medical College were already thriving also, but they were then in limbo and their students were not accepted.

Agnew was strongly opposed to women medical students. He admired the domestic virtues of a lady and believed a woman should be taught housekeeping, hygiene and the fine arts. After that, he said, the more she knew the worse off she was. But this was the era of militant woman's suffrage. Elizabeth Blackwell had already succeeded in obtaining a medical education, even though she had been spurned in Philadelphia. Hospitals were only used by poor people, paupers, objects of charity and social outcasts, so that there was a great deal of venereal disease and urologic material among the clinical patients used in teaching. This was embarrasing to patients, professors and students when there were women in the audience. The students were hard to control and the lecturer was inhibited in what he could say. This was at the height of the Victorian Age! S. Weir Mitchell, in his obituary of Agnew, said: "He believed, as I do, that a clinical class of men and women is disgusting. He thought it wrong and sacrificed the coveted surgeoncy at the Pennsylvania Hospital—resigning at once rather than obey the order of the managers." For a few years immediately before the Civil War, the Penn Medical University, one of the several ephemeral medical colleges of Philadelphia during the nineteenth century, taught women, but separately in alternate terms. Soon after the Civil War, the Pennsylvania Hospital managers became converted to feminism and by 1869 were allowing women to attend lectures there. Alfred Stillé in 1869 spoke a few words of welcome to the female students in the audience, but the men students rioted and the medical faculty of the city printed a *Remonstrance* against mixing the sexes in medical student groups. Agnew, in his introductory lecture the following year, then expressed his strong opposition. When the Board of managers of the Pennsylvania Hospital insisted, he resigned in 1871, to relent six years later, when he was reinstated. At the Medical School of the University of Pennsylvania he carried greater weight in formulating policy, and it was not until 1913 that mixed classes were accepted there. The women were not without friends at the University, however; in 1884, Horace Jayne, a wealthy medical alumnus who was a zoology "buff", set up a biology department at Penn, became its first director and admitted women without discrimination. Even before that, in 1877, women were accepted by the Auxiliary Medical Faculty of the University of Pennsylvania which was a department for graduate studies in the specialities, and a graduate of the Woman's Medical College earned her Ph.D. in 1880, which was the first University of Pennsylvania degree ever awarded to a woman. Dr. William Pepper was in favor of higher education for women and did not sympathize with his friend Agnew, or with Sir Benjamin Brodie who

said he never saw a girl with a schoolbook in her hand without feeling a strong desire to throw it at her head! But the Medical School held out until the second decade of the twentieth century.

Agnew was a great advocate of extramural teaching. There was an autumn course of medical lectures from 1868 to 1872 at the University of Pennsylvania which then became the Summer Medical Association of the University where the specialties were taught. Agnew taught surgery, Norris and Strawbridge eye and ear, and Duhring dermatology. But Agnew never became a full-fledged specialist. He covered the entire field of surgery and almost all of medicine. He believed a medical man could be a good physician without any knowledge of surgery, but that a good surgeon had to be a good medical man too, because the surgeon has to watch and study and care for the medical conditions liable to be present in every surgical case. In later life he could not refuse medical cases in families who had been accustomed to depend upon him for years, and even to the time of his death he had a large consultation practice in strictly medical diseases. He did abdominal, gynecological, orthopedic and even brain surgery, and was as ready to set a fracture as to cut for a stone, even after his younger assistants, White and Willard, had set up special departments of urologic and orthopedic surgery. William Goodell, another famous son of Chester County, kept for himself the chair of Women and Children, but Agnew was a skilled gynecologist in his own right. For many years Agnew was one of the best ophthalmic surgeons in the city and in 1863 was appointed surgeon to the Wills Eye Hospital. In 1867 he was appointed to the surgical staff of the Orthopedic Hospital of Philadelphia. He also took an active part in the development of the Presbyterian Hospital where he was appointed Honorary Surgeon.

In his practice Agnew went to the home of the patient to operate if necessary. He would make as many as ten or fifteen calls in different parts of the city, in addition to his office and hospital work, lectures, and so on, and then might travel all night to a distant city. J. William White mentions a case in which he operated for stone in the bladder in a little town in the southern part of Delaware, which means that he must have gone by train part of the way and by horse drawn vehicle the rest. My own chief, Dr. Atlee, nearly half a century later, likewise did not hesitate to operate in the patient's home when it was necessary. An appendectomy might be done with the patient stretched out on the kitchen table and a member of the family or a neighbor pouring the ether.

A West Chester newspaper on September 19, 1873 had a news item about a distinguished visitor, Professor D. Hayes Agnew, who came on professional business, and reminded its readers that this man, whose surgical skill was known throughout the entire country, was originally a Chester Countian, recalling the iron business which it stated had been located on "Thunder Hill" on the New London Road not far from Elk Creek. Early one morning he was called by telegram to an isolated place in the northern part of Pennsylvania. He ate a hurried breakfast, caught his train and by dint of close railway connections and a final drive of eight miles over rough road, reached the house of his patient late in the afternoon. An operation was required, which he performed at once while a meal was being prepared for him. On looking at his watch and timetable he decided to forego the meal, made a train that enabled him to connect with one in Harrisburg to reach Philadelphia in time for office hours and his lecture the next morning. He had great stamina until nearly the time of his death. When operating in private homes he lifted patients from bed to a table with the aid of whoever might be around. There were no elevators; he usually flew up the

stairs at the hospital at a gait that winded his assistants. He inspired confidence in his students and patients and his associates admired and respected him; many were indebted to him for instruction and advancement. His love for work, years of study and teaching, marvelous patience and remarkable stoicism all combined to make him the master surgeon. (Boerhaave is said to have left, when he died, one great precept for success in medical practice: Keep your feet warm, your head cool and your bowels open.) Once, during an operation for hemorrhoids at the Bingham Hotel in Philadelphia, the patient, who was apparently well and strong, had taken less than four ounces of ether, when he suddenly stopped breathing. In spite of all efforts to resuscitate him, he died. Dr. White, who had assisted, was pretty badly shaken, but Agnew passed it off, outwardly unperturbed, as a statistical inevitability. "I've no doubt passed my numerical limit long ago", he mused stoically, as he walked to his carriage waiting on the street. Autopsy later proved that death had been coincidental, due to a cerebral apoplexy.

In 1854 Agnew obtained the post of surgeon to the Philadelphia Hospital at Blockley where there was abundant clinical surgery for him to do. He was also appointed curator of the pathological museum. Post-mortem material was plentiful for the basic research he required and he developed a strong following of students in gross morbid anatomy, the knowledge of which is so essential to effective surgery. He was an important member of the Philadelphia Hospital staff and wrote a good history of the institution. Though greatly interested in pathology, the microscope was of little use to him, because it was not until Ehrlich's methods of tissue staining developed that microscopic techniques opened new fields in the study of hematology, microbiology, cancer, and so on. The old surgical building at Blockley was dark, poorly ventilated and, until 1866, not connected to the main hospital buildings so that patients had to be carried out in all kinds of weather. A new building, the Agnew Surgical Amphitheatre, was opened in 1892. The autopsy building nearby was converted into the Osler Museum in 1932 and has been carefully nurtured ever since by Dr. Robert Hunter who lives in a charming old farmhouse on Fisherville Road in Chester County not far from here.

In 1858, Dr. Henry Hollingsworth, the Professor of Surgery at Penn, enlisted the aid of Agnew to lecture to his students when he was unable to do so himself. For five years Agnew thus lectured frequently, but unofficially, at the University. His first official appointment came on December 21, 1863, as Demonstrator in Anatomy, a subsidiary position to the Professor of Anatomy, Dr. Joseph Leidy. He brought many of his paying students with him to Penn. After six years, he grew restive as a subordinate and threatened to quit unless given faculty status. By this time (1870) he was one of the leading surgeons in America, his fame equal to that of Pancoast and not far behind that of Gross, both of whom were at Jefferson Medical College. Smith, at the University of Pennsylvania, was popular but did not possess the surgical showmanship nor the pedagogical wizardry of Gross or Agnew. Penn decided to meet the serious competition from Jeff and appointed Agnew Professor of Clinical Surgery, with the additional appellation of Demonstrative Surgery, to assure him the right to teach operative surgery on the cadaver, as well as the responsibility of lecturing to the class as he operated. The next year Dr. Smith retired and Agnew succeeded to the senior chair of surgery, a chair originally occupied by Philip Syng Physick. Six years later, in 1877, Mrs. John Rhea Barton, widow of an esteemed Pennsylvania Hospital surgeon, born in Lancaster County, Pennsylvania, created the Barton Professorship of Surgery by a

gift of $50,000 to the University of Pennsylvania. This was the first endowed medical professorship and D. Hayes Agnew was its first incumbent. Deaver, Frazier, Eliason, Ravdin and Rhoads have successively occupied this illustrious chair—all within my own memory.

Agnew was active in the establishment of a state board of medical examiners for licensure of physicians. This was proposed by the Pennsylvania State Medical Society in 1888 and finally passed in 1893, and led to lengthening the medical course at Penn to four years. In 1881 a step in this direction had taken place when a law was enacted by the state to register all practicing physicians. Before that time a medical diploma signed by the professors of any medical school conferred the right to practice, and medical schools of all kinds and cults were sprouting everywhere.

Agnew's most famous patient was President Garfield. The President was shot by a madman on July 2, 1881. In spite of attempts by a number of doctors to reach the bullet with their fingers, or with instruments, he rallied and seemed to be doing well until infection set in. Five leading physicians were called into consultation, among them Dr. Agnew, to whom all deferred as the most expert. Strongly antislavery, he had entered upon active military service during the civil war and developed great skill in treating gunshot wounds at the military hospitals in Philadelphia. At Gettysburg he had charge of the case of General Hancock, who was Garfield's opponent in the election of 1880, so that both candidates for the presidency were his patients. In Garfield's case he advocated masterful inactivity to the end. The damage had been done before he ever saw the patient and no one was ever able to locate the bullet positively until the autopsy. A West Chester newspaper on July 30, 1881, reporting the natural excitement around Agnew, stated: "All eyes are centered on Dr. Agnew in this sad ordeal of national affairs.... Don't you Chester County people feel a sense of additional pride in having, in the person of the doctor, one of your gifted sons? Philadelphia is indeed proud of owning him by way of adoption and little Atglen (later Penningtonville) up the Pennsylvania Railroad and near to where the seam which joins Lancaster and Chester Counties occurs, has every reason to feel honored at being his birthplace." On September 23, 1881, four days after the president's death, Agnew visited West Chester and was guest of Dr. Isaac Massey, with whom he, as well as Drs. Price, Hartman and Brinton, dined. During his stay, the paper reported, Dr. Agnew held a consultation with Dr. Massey in reference to an important case in this borough, and he had a chat with the West Chester doctors about President Garfield's injuries and death which was said to be exceedingly interesting. Among other things he discussed the "little instrument invented by Alexander Graham Bell to ascertain the whereabouts of the ball." This alluded to an electromagnet by which Bell was actually able to pinpoint the location of the bullet, but it was not possible to be certain from clinical observation, and it would have been dangerous to attempt surgical removal because of the location and infection. "When a bullet is placed in the mouth," Agnew explained, "and the instrument placed on the cheek, the latter will tick so loudly that it can be distinctly heard at a distance of three feet."

In caring for the President, Agnew spent almost all his time, for three months, in Washington and later at Elberon, N.J. His office was closed and he discontinued his practice, then probably the largest and most lucrative ever acquired by an American surgeon. When it was all over Congress voted him a fee of $5,000, which Mitchell thought was niggardly, saying he could have made as much in a single large operation done in any large city.

When Dr. Agnew reached his fiftieth

year in practice in 1888, two hundred people attended his jubilee, at which Jacob Mendes Da Costa, Professor of Medicine at Jefferson Medical College, presided. Agnew had presided in 1879 at the jubilee of his friend, Samuel D. Gross, and at that time had lauded the deeds of senior citizens, citing Plato at eighty-one, Isocrates at ninety-six, and old Fabius, the Roman general who, in advanced age, was more than a match for the youthful Hannibal. Thomas Eakins painted the canvases of Gross in 1875 and of Agnew in 1888 which are now on exhibit at the Philadelphia Museum of Art.

Agnew had entered the practice of medicine eight years before anesthesia and whenever he told his class about the suffering he had seen under the knife his voice would tremble. The British surgeon Joseph Lister began to publicize antiseptic surgery in 1867 and Agnew, who met him personally on his visit to Philadelphia in 1876, became one of the first American exponents of this advance. At first it consisted of spraying carbolic, so that a picture of Agnew's clinic in 1886 still shows him and his assistants in the operating room wearing street clothes just as in the Eakins picture of the Gross clinic. In Eakins' painting of Agnew, however, the surgeon is conspicuous for the clean gown he is wearing. It was not until 1890 that Halsted introduced rubber gloves into the surgical theatre. The Eakins picture gives evidence of the new emphasis on asepsis. It was presented to Agnew by Joseph Alison Scott for the graduation class of 1889—at the same commencement exercises at which William Osler gave his famous valedictory, Aequanimitas. No one could better exemplify this superb quality of imperturbability than the great surgeon then being honored, D. Hayes Agnew.

Agnew suffered from diabetes and angina pectoris during the last years of his life, but worked until within a few days of his death at the age of seventy-four. Teacher, surgeon, humanitarian, he had lived a full life, and friends, praise and honors came to him in full measure. At his jubilee, Dr. S. Weir Mitchell read a poem in which he outlined the promises made to him by the Goddess of Learning:

> But I will take you where the great have gone
> And I will set your feet in honor's ways;
> Friends I will give you and length of crowded years,
> And crown your manhood with a Nation's praise.

Felice Fontana (1720–1805): The Forgotten Physiologist[1]

By JOSEPH R. DiPALMA, M.D.[2]

THERE are some great men who through some quirk of fate fail to achieve outstanding recognition in history despite crucially important contributions. Such a man was Felice Fontana. Born in 1720, in the town of Pomarola near the Italian-Austrian border, he was destined to anticipate some of the greatest discoveries of modern medical physiology which are, however, generally attributed to later "greats." This brief report will give some details of his life, an account of his pertinent works, and will attempt to find some reasons for his relative obscurity.

Little is known of Fontana's childhood. In order to gain an education he entered the clergy as was the custom in those days. At various times he received education at the ancient universities of Verona, Parma, Padua and Bologna. However, he discharged no spiritual functions and remained a lay clergyman as typified by Spallanzani or much later by Mendel. He could therefore be called an *abbot* or *abbé* or *abbate*. In a sense in his day he had what we might today call a "Career Investigationship". Demonstrating at an early age outstanding gifts of the mind and personality, he was awarded the Chair of Philosophy at Pisa. Some time later he was appointed Director of the Museum of Physics and Natural History at Florence by the Grand Duke of Tuscany (Leopold II). Here he spent the greater part of his productive life interrupted only by the events of the French Revolution. On the whole, the environment in which he worked was one of a small principality or city-state. Italy was not to be unified for more than a century and strong feelings of national pride did not exist. Nevertheless, the 18th Century was one of awakening and in Fontana's position in Florence he might be considered to have been in the center of the intellectual milieu. The rigid scholastic dogma of the previous century was beginning to be relaxed. Fontana was greatly influenced by the recent discoveries of Newton and indicated in his writings that he himself followed the famous quotation from the great scholar:

> "The origin of all laws of Nature is such that to the wisest judgement no vestiges of necessity are apparent. These we must seek not by invention and conjecture but by observation and experiment."

No portraits of Fontana exist. Figure 1 shows a pen and ink sketch of a medallion made in later life. There are several biographies, all in Italian, of which by far the best is that of G. Bilancioni (1). This reference gives an extensive account of his scientific work. In America, Fielding H. Garrison (2) has written an illuminating editorial on Fontana, and Hebbel E. Hoff (3), a prominent contemporary physiologist, has done much to bring modern recognition to the "forgotten physiologist."

To begin with, it is well to comprehend that Fontana was one of those universal types of geniuses who were equally at home in philosophy or in art, in theory or in practice. We are concerned here only with his contributions to physiology, but he is equally famous for his originations and creations in anatomy, pharmacology, biology, botany and clinical medicine.

[1] Read before the Section on Medical History, The College of Physicians of Philadelphia, 9 March 1965.

[2] Professor and Chairman, Department of Pharmacology, The Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania 19102.

FIGURE 1

He began his contributions to physiology because of his great interest in the teachings of Albrecht von Haller. These concerned the controversies about the subject of irritability. It was the custom to explain muscular movement, the senses, and indeed all bodily functions by the flow of animal spirits, a concept stemming from the ancient Greeks. Haller laid down the elementary principles of excitation, but it was Fontana who clearly recognized their significance. By a series of ingenious experiments in intact animals and on nerve muscle preparations, he deduced the following laws:

1. Every contraction of a muscle fiber requires a new stimulus.
2. The stimulus merely fires or sets off the response—it does not produce it.
3. The act of the response itself destroys irritability.
4. Relaxation of a muscle is a positive phenomenon. It is the act of relaxation which restores irritability.
5. There is a period of time before a tissue will respond to a second stimulus and this period of time varies with different organs and is appropriate to that organ's function (refractory period).

From the viewpoint of modern neurophysiology and biology, these laws appear elementary and self-evident. However, in Fontana's time it was actually believed that a fluid flowed along a nerve into a muscle each time it was excited. Fontana's comprehension of excitability and refractory period was admirably illustrated by his explanation of the heart beat. He correctly interpreted the refractory period of the heart as the important function which permitted filling of the chambers during diastole. Figure 2 shows the frontispiece of Fontana's second publication written in Italian on the subject of irritability. In this communication he pays a touching tribute to Haller.

In other studies Fontana clearly defined the difference between voluntary and involuntary movements, and practically defined the modern concept of the reflex arc. Fontana, without realizing it, also described the autonomic nervous system. Hi-

PARTE I.

DELLE LEGGI

DELLA

IRRITABILITA MUSCULARE

CAPITOLO I.

LEGGE I.

Ad ogni contrazione della fibra muſculare è ſempre neceſſario un nuovo ſtimolo, che ne riſvegli l' irritabilità.

§. I.

NOn ſarà certamente impreſa facile, come forſe taluno potrebbe immaginarſi, l'eſaminare le leggi di quella nuova proprietà della fibra animale, che dall'Hallero, il quale è ſtato il primo ad illuſtrarla con nuove, e belle eſperienze, è chiamata irritabilità Halleriana. Imperciocchè niente di più ſi è ſaputo finora, ſe non che la fibra animale ſtimolata che ella ſia, per un'inſita proprietà, come ſi crede, ſubito ſi contrae.

a Qua-

FIGURE 2

experiments on the iris and the light reflex of the pupil were the first comprehensive demonstrations of these phenomena. Incidentally, physicians may perhaps recall that when they studied anatomy the small spaces in the angle of the eye which conduct the aqueous humor from the anterior to the posterior chamber were called the "Spaces and Canals of Fontana." It is deplorable that this is the only frequently mentioned modern reference to the great man.

One other outstanding physiological concept first expounded by Fontana belongs today more to the field of pharmacology. In the course of his duties Fontana was commissioned to study the action of snake venoms. The prodigious experiments he performed hardly seem credible and alone would establish him as a foremost investigator, even in modern times. After over 7000 experiments on different snake venoms on various animals and even on himself, he came to certain conclusions (4). Snake venoms are of two main types, neurotoxic and hemotoxic. Snakes are immune to their own venom. The venom must be administered parenterally to be toxic. This latter point he proved by ingesting snake venom himself! However, the important principle he derived was that poisons have *a locus of action*. This startlingly modern viewpoint took several centuries to be clearly understood and is, of course, today a basis of comprehension of the action of drugs (5).

The work of Fontana covers many fields. For example, he anticipated the site of action of curare to be the neuromuscular junction by nearly 100 years prior to the great Claude Bernard. Certainly, if versatility were a sign of genius Fontana would carry first honors. Unfortunately, it is this very profusion of effort which confuses posterity. Had he concentrated and consolidated but one area, perhaps he would be more esteemed. This is not, however, the main reason for the general ignorance of Fontana's contributions. He lived a little too early to partake in the main stream of the scientific revolution. The great resurgence of physiological investigation began about 50 years after his death. Few who picked the plums later on gave credit to the pioneers who planted the trees. It may be argued that Fontana should have published more widely and communicated with the scientific societies of other countries. This he failed to do. In his defense it must be recognized that a great deal of his time and effort were expended in the fastidious and detailed construction of a museum of anatomical wax specimens. These were greatly admired by his supporters, but are of little interest to modern anatomists.

Whatever the reasons for the obscurity of Fontana as a physiologist, he did achieve considerable fame in his own time. He died in 1805 at the ripe age of 85, having worked productively to the end. His remains may be found in the Florentine Pantheon, Santa Croce, among many illustrious contemporaries. Perhaps some scholarly medical historian may yet write a history of physiology which places proper value upon the contributions of this modest and versatile genius.

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Library Historical Notes

By W. B. McDANIEL, 2d, PH.D*

THREE recent acquisitions revived pleasant memories in the fellowship of the College, as in the library's historical department:

1) The publication of "A History of Ophthalmology at the University of Pennsylvania" (Springfield, Ill., C. C Thomas, 1965), by Daniel M. Albert, M.D., and Harold G. Scheie, M.D., while designed primarily as a contribution to the University's celebration of the Bicentennial of its School of Medicine, gives us, in effect, a valuable history of ophthalmology in Philadelphia from the days of Philip Syng Physick to the present. The inevitably close link between the College and this Department of the University may be partially illustrated by recalling that all of the five successive chairmen of the Department—Drs. William F. Norris, George E. de Schweinitz, Thomas B. Holloway, Francis Heed Adler, and the senior author of the book, Harold G. Scheie—served as chairman of the College's Section on Ophthalmology; that the library's current-periodicals room bears the name of Dr. Norris; that Dr. de Schweinitz also served as President of the College; and that Dr. Scheie recently headed its Finance Committee. It will be obvious, therefore, that the College library was able to make some contribution to the book's documentation —a circumstance graciously acknowledged by the authors in the book and in the material form of presentation copies of it.

2) A group photograph of "Three Doctors who have practised medicine in Germantown for nearly fifty years"—Drs. James Darrach (1828–1923); Robert Norton Downs (1830–1920); and William Rush Dunton (1831–1911). On the back of the picture is penned the following note: "This picture was much valued by Sir William Osler and hung in his Consulting Room in Oxford—Sent to Dr. McKane Downs [*i.e.*, Dr. Thomas McKean Downs, 1894–1960] July 1923 by Grace Revere Osler Oxford". Osler had doubtless become acquainted with the three elderly Germantown physicians through his and their fellowship in the College, and their joint membership, also, in the Philadelphia Pathological Society. The picture was kindly presented to the College by Mrs. Rowland Evans (sister of the late Dr. T. McKean Downs), at the suggestion of an astute Fellow, Dr. Frederick C. Sharpless.

3) W. S. W. Ruschenberger's "Narrative of a voyage round the world, during the years 1835, 36, and 37; including a narrative of an embassy to the Sultan of Muscat and the King of Siam." 2 vols. London, 1838. Recalled today most frequently as the author of "An account of the institution and progress of the College of Physicians of Philadelphia during a hundred years, from January, 1787", Phila., 1887, Dr. William Samuel Waithman Ruschenberger (1807–1895) was a President of the College (1879–1882) whose colorful career and varied talents would seem to entitle him to considerably more attention than posterity has accorded him. In his younger days, while a naval surgeon, he wrote two travel books which "were widely read and were republished in England". The library, curiously, had neither one of them, though it had the scrapbook apparatus for the one with which we are here concerned. For many years we have been piously striving to fill these family lacunae. A decade or so ago, a copy of the earlier book was found in a hospital in the area which

* Curator, Library Historical Collections.

Downes
Dunton
Darrach.
Three Doctors who have practised medicine in Germantown for nearly fifty years.
"Behold how good and joyful a thing it is, Brethern to dwell together in unity"
Psalm cxxxiii

FIGURE 1

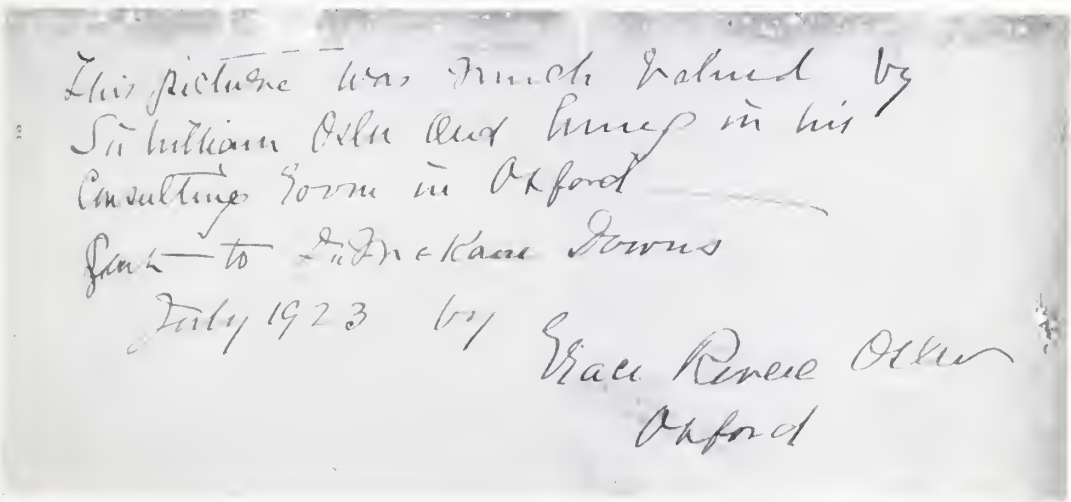
This picture was much valued by
Sir William Osler and hung in his
Consulting Room in Oxford
Jan 1 — to Dr McCrae Downes
July 1923 by
Grace Revere Osler
Oxford

FIGURE 2

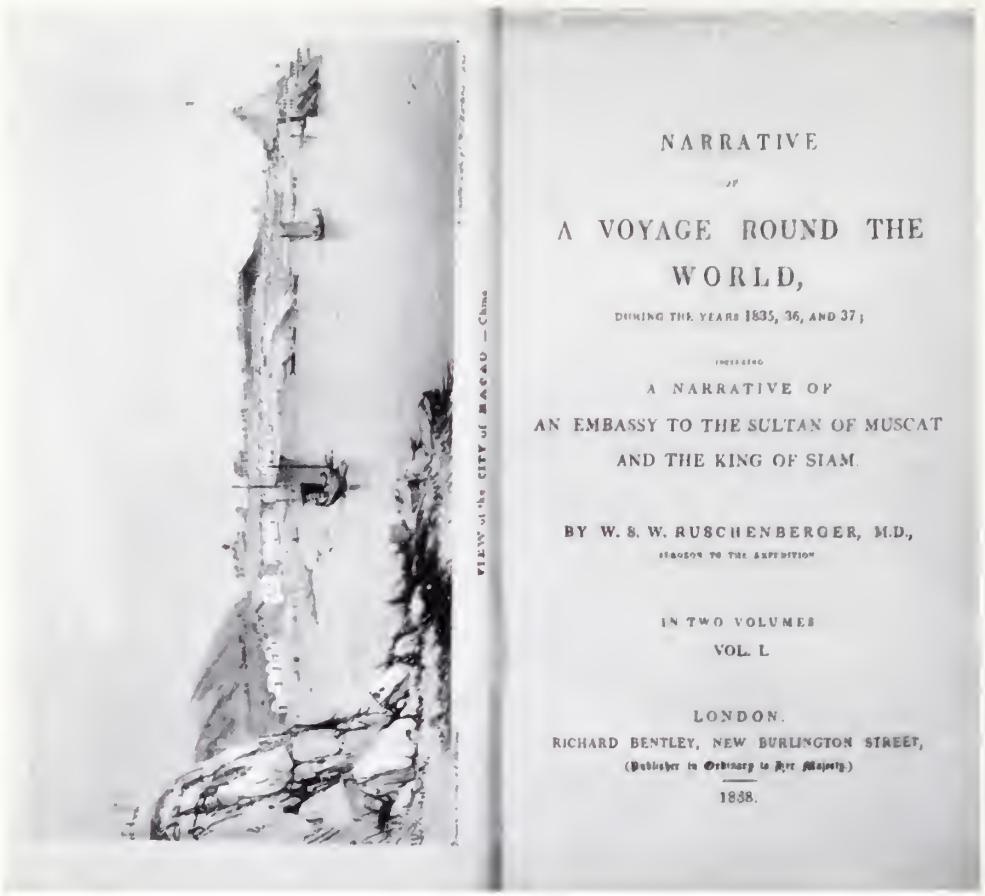

FIGURE 3

had invited us to help ourselves to any of the older peripheral material in its library. And now our purchase of the 2-vol. "voyage round the world" from a London bookseller brings the search to a full conclusion. The considerable price asked for the work must be attributed less to its handsome modern binding than to a degree of rarity that goes far to explain the length of the search.

A Decade of Harvest: *Ave atque vale* to the Editor, Fred B. Rogers, M.D.

By W. B. McDANIEL, 2d, PH.D.

AN editor is doubtless regarded as a sometime thing by the non-literary minded, while their opposites tend, on occasion, to regard him as an insensitive despot. Despite the variable degrees of appreciation—non-existent, negative, and positive—accorded the efforts of individual editors, the editorial survival rate is probably as respectable as those obtaining in most of the other authoritative professions. In the sixty-five-to-six years of the present century, for example, the *Transactions of The College of Physicians of Philadelphia* has had but seven successive editors. The first of these, William Zentmayer, M.D., edited 14 of the annual volumes (as well as the final one of the preceding century); the second, Walter G. Elmer, M.D., masterminded the next 19 volumes. The third, J. Harold Austin, M.D., and the fourth, Thomas Fitz-Hugh, Jr., M.D., laboring in one of the temporarily troubled periods in the College's history, edited, respectively, but 3 and 2 volumes. The mantle was then placed—possibly for the first time forthrightly—on a non-Fellow of the College, its then Librarian, W. B. McDaniel, 2d, PH.D., who edited the next 17 volumes, and during whose tenure the journal assumed its quarterly schedule and present title. He was succeeded by another non-Fellow and member of the library staff, Mr. William K. Beatty, whose call to a higher station away from this city permitted him to edit but a single volume.

Then, in April, 1956, the College administration was fortunate enough to find, again, a Fellow able and willing to serve as its editorial ambassador to the world-at-large. This was, of course, Fred B. Rogers, M.D., who had been elected to the fellowship, at the age of 28, only fifteen months before. His retirement from this strenuous, year-around responsibility on publication of this final number (April, 1966) of his 10th volume has generated the present attempt, by his only surviving local predecessor, to recall a few of the editorial fruits garnered in this decade of harvest. The attempt draws on data gleaned from the volumes themselves, and on the numerous opportunities afforded for personal observation of the editorial methodology that has prevailed during the period under review.

The task of assembling material for the quarterly issues of this journal is one of the editor's major ones, for little of the material comes to his desk under its own steam. The chief sources of supply must be, obviously, the annual series of endowed lectures; presentations at the meetings of the several Sections of the College; and annual reports from the officers and departments of the College. The obtainment of these is in no sense automatic, as indicated. The Editor, to fill his basket attractively, and with an eye to its present and potential use as an historical record, must maintain eternal vigilance over the programs of the College and its Sections, and over activities of its departments that might warrant special editorial attention. When judgments on publishing viability have been made, considerable time and effort often must then be expended in shaping the desired texts into a form adapted to printing practices. Dr. Rogers' vigilance, judgment, pertinacity, and persuasive powers are firmly documented in these ten volumes by the presence of an extraordinarily high percentage of the important

endowed lectures; by the selection of papers read before one or another of the Sections; and by a clean sweep of abstracts of the 195 presentations before the Section on General Medicine. One notes with interest that Dr. Rogers, himself, was author or co-author of seven of the papers read before the latter Section, their varied topics—anthrax, arthritis mutilans, botulism, hypoparathyroidism, Q fever, salmonellosis, typhoid fever—reflecting his work in hospital and clinic.

During this decade, two medical-student essay contests were established by Sections of the College: 1) The Edward Bell Krumbhaar Prize in Medical History (1957), by the Section on Medical History; 2) The William Harvey Perkins Prize in Preventive Medicine (1960), by the Section on Public Health, Preventive and Industrial Medicine. It is characteristic of the editor's broad vision that, to date, seven of the Krumbhaar Prize, and six of the Perkins Prize, student-authors have received the stimulation of seeing their essays in print, in the *Transactions & Studies*. In like manner, two older Section lectureships—the Kate Hurd Mead, and the Arthur Parker Hitchens—were given full historical shape, through editorial enterprise, by belated publication of several of their earlier lectures.

The needs of medical historians have been further, and significantly, served in recent years by publication of some independent studies based primarily on material in the library's historical collections. Particularly notable, in this category, is the series of eight articles on the *Extinct Medical Schools of Nineteenth Century Philadelphia*, by Harold J. Abrahams, PH.D., the first Research Associate of the library. Again, the "Bicentennial of Medical Education in the United States" was signalized by publication of scholarly annotated translations of the Edinburgh medical theses of John Morgan and Benjamin Rush, pioneer academic medical teachers in this country, and numbered, also, among the founding Fellows of this College.

The wide attention accorded the journal while under Dr. Rogers' aegis could be demonstrated by citing the numerous authorized reprintings of material that first appeared in it. The retiring Editor, as it happens, is a Navy veteran. It seems fitting, therefore, to accord him at this time a verbal salute that must be familiar to him —Well done!

Memoir of Lovett Dewees 1880–1965*

By EMILY HARTSHORNE MUDD, PH.D.

LOVETT DEWEES was born on 17 January 1880 in Westtown, Pa., into a Quaker family. His father was well known as a teacher in the Westtown School, from which Dr. Dewees graduated. His college was Haverford, followed by graduation from the School of Medicine, University of Pennsylvania, in 1907.

In his years as a respected general practitioner on the Main Line, Dr. Dewees early became interested in the practical and emotional problems of his families. Much of his time was filled in delivering babies and caring for them as they grew and for their parents. His empathy for those mothers whose continued pregnancies depleted their health and propounded anxieties and difficulties in their sexual adjustment led him to pioneer in exploring and making available to his patients methods of child spacing. He initiated with others the opening, in 1927, of Philadelphia's first Birth Control Clinic, a move which at that period took more than considerable courage.

Innumerable hours of sympathetic listening to the problems of both his men and women patients and their adolescent young people led Dr. Dewees to participate actively in the founding in 1933 of both the Marriage Council of Philadelphia, which offered pre- and post-marital counseling, and later the Marriage Council of the Yearly Meeting of the Religious Society of Friends. He served as President of the latter organization for many years. His sponsorship of these centers included the acceptance of referrals for premarital examination, an aspect of his practice in which his skill and success won wide acclaim and brought to him many requests from Departments of Obstetrics and Gynecology for lecturing and demonstrating to medical students and medical societies. Dr. Dewees' article in the Journal of the A.M.A. in 1938† was their first to be published on a series of contraceptive cases with careful followup. The pursuance of new knowledge in these fields led Dr. Dewees to work closely with national groups, including the National Committee on Maternal Health, The American Association of Marriage Counselors and the Human Betterment Association.

Dr. Dewees had an unusual perception and interest in a preventive approach and a sincere conviction in the efficacy of education. This broad perspective enabled him also to teach in undergraduate courses in preparation for marriage at leading schools and colleges, among which were George and Westtown Schools and Haverford College, Temple University and University of Pennsylvania. In this last he held a staff appointment in the Department of Obstetrics and Gynecology.

In addition to these special interests, Dr. Dewees' civic perspective and commitment involved him as a founder of the Main Line Health and Welfare Council and as Chairman of the Board of Health of Haverford Township. He served also during his medical career as Consulting Physician at the George and Westtown

* Read before The College of Physicians of Philadelphia, 1 December 1965. Prepared and published at the request of the Council of The College of Physicians of Philadelphia. Dr. Mudd is Professor in Family Study in Psychiatry, University of Pennsylvania School of Medicine.

† Dewees, L., and Beebe, G. W.: Contraception in Private Practice—12 Years Experience, *Journal of American Medical Association* **110**: 1169–1172, April 9, 1938.

Schools, at Bryn Mawr and Haverford Colleges, and at Bryn Mawr Hospital.

Dr. Dewees gave of himself unstintingly, asking little in return beyond the satisfaction he felt in his work and friendships. During his later years he was one of the first to be honored as a "Distinguished Alumnus" by the Medical School of the University of Pennsylvania. Bryn Mawr Hospital and the Pennsylvania State Medical Society cited him respectively for twenty-five and fifty years of devoted service to his community and his profession. In 1964, after blindness made it impossible for Dr. Dewees to function in the clinic, the Planned Parenthood Association of Philadelphia designated that their clinic rooms at 2004 Walnut Street should be called the Lovett Dewees Clinic and that a plaque to this effect be displayed in the building.

New and novel ideas never startled Dr. Dewees or shook his calm exterior. Unusual suggestions, extremes of behavior, acts unacceptable to conventional souls took their place in his broad spectrum of tolerance for human difference, of sympathy for his patient's pain, of dedication to make things better, and of fearless, selfless searching as to how this could be achieved. These characteristics, together with his keen intelligence and his persistence, led him to experimental procedures well in advance of his profession and his community.

Dr. Dewees believed in women and pioneered in enabling them to be persons with justifiable control and pride in their bodies as well as their minds. He was *with* his patients the whole way, and his patients thought of him as their friend and their family's friend. His was the quiet, unostentatious, steady, pushing at the unopened gates of the future. His was the humility of the great of heart and of spirit.

Lovett Dewees' death on 15 January 1965 removed a true humanitarian from our midst. He is survived by his widow, Mrs. A. Lovett Dewees of Swarthmore, Pa., and three children, Mrs. Nancy H. Flash of Brunswick, Me., Mr. Allen H. Dewees of Denver, Colo., and Robert L. Dewees, M.D., of Wilmington, Delaware.

Memoir of Alexander Garrison Fewell 1884–1965*

By WARREN S. REESE, M.D.

ALEXANDER GARRISON FEWELL was born in Ebenezer, now a part of Rock Hill, South Carolina, on January 8, 1884. He retired from active practice because of ill health in 1961. He died on January 4, 1965, four days short of his eighty-first birthday, twenty-seven years after the death, and at the same age as the man who had persuaded him to study ophthalmology, and became his admired Chief and revered friend, Dr. George E. de Schweinitz.

Dr. Fewell's high school days were spent at a private academy near his home. He then attended the Presbyterian College in Clinton, South Carolina, this school having been chosen by his father as football was not played there, but Dr. Fewell, in his sophomore year, early showed his independence, individuality and organizational ability when he started a football team and became its star fullback! It was during this time that he definitely decided to study medicine, following in the footsteps of a greatly admired uncle.

Following graduation, four years later, he taught Latin and Greek in a boys' preparatory school in a nearby town for two years.

He then entered the Medical School of the University of Pennsylvania, graduating in 1910, and served his internship at the Methodist Hospital in Philadelphia. Following this, he returned to his home town to enter general practice, but soon decided that this was not his forte.

A rather unique experience hastened this decision. He was summoned one cold, wet evening by the husband of a young colored woman, to come assist at the birth of their first child. After driving many miles out into the country in those horse and buggy days, they found the woman in the throes of labor. It proved to be a breech presentation, the first that Dr. Fewell had managed alone, and after prolonged labor delivery was accomplished, but at that moment the young husband who had been holding a kerosene lamp suddenly fainted and the house was engulfed in flames, Dr. Fewell being obliged to drag the two adults and a screaming baby out into the cold rain!

He then returned to Philadelphia and was considering pediatrics as a specialty when he was persuaded by the famous Dr. S. Weir Mitchell to journey to California to take charge of a young man totally incapacitated from encephalitis. While there, he renewed his acquaintance with Miss Alice Urquhart whom he had met in Philadelphia during his medical school days and they were married on August 12, 1915.

The sudden death of his young patient in 1916 ended this phase of Dr. Fewell's career and he returned to Philadelphia once again. He then had the good fortune to come under the influence of Dr. de Schweinitz and entered the Polyclinic Hospital for graduate study in ophthalmology. On completion of this course, in 1917, he entered the United States Army Medical Corps, shortly thereafter sailing for Paris, France, where for eighteen months he served at the American Ambulance Hospital. One of his patients was Floyd Gibbons, the well-known war correspondent whose one eye Dr. Fewell saved but was

* Read before The College of Physicians of Philadelphia, 3 November 1965. Prepared and published at the request of the Council of The College of Physicians of Philadelphia.

obliged to remove the other, and who expressed his gratitude for Dr. Fewell's treatment in his novel entitled, "And They Thought We Wouldn't Fight".

After being promoted to a Captain he sailed from France at the termination of the war, being assigned as private physician to the then Secretary of the Navy, Franklin D. Roosevelt.

Soon after his discharge from the Army in 1919 he accepted the position of Associate in the office of Dr. de Schweinitz, succeeding Dr. Thomas B. Holloway, a position he held until Dr. de Schweinitz' death in 1938.

I first met Dr. Fewell briefly while a resident at the old Wills Eye Hospital shortly before he entered the Army, but did not learn to know him well until after the War when he joined Dr. Holloway's Clinic in the same hospital where I was working in Dr. Zentmayer's Clinic.

Following Dr. Holloway's death, he served for one year as Chairman of the Department of Ophthalmology at the University of Pennsylvania. During his career, he was Chief of Ophthalmology at the Episcopal, Pennsylvania and Children's Hospitals; and while at the University, he worked with the late Dr. Charles H. Frazier as a member of one of the first famous neurosurgical teams in this country. As a result of this latter experience, he was, I believe, one of the first to emphasize the value of tarsorrhaphy in the treatment of neuroparalytic keratitis.

When the Polyclinic Course and the Medico-Chirurgical College were taken over by the University of Pennsylvania to form the Graduate School, he served as a lecturer, teacher of refraction and of clinical ophthalmology, particularly ophthalmoscopy, thereby earning a much deserved Professorship. He was very proud of his association with the Graduate School, and also with Dr. Holloway, its first Dean of Ophthalmology.

Dr. Fewell was also proud of having been one of the founders of the Ophthalmic Club; indeed, I think he may have suggested its organization.

He was liked by his clinic subordinates because of his kindness and consideration, and the unstinting time he gave to his work, and to the best of my recollection, was always serving at least two clinics.

Although not a prolific writer, probably because of the time entailed by clinic work and teaching, he was really a work horse in ophthalmology. He helped Dr. de Schweinitz with many of his papers, notably the Bowman Lecture, and he told many amusing stories about his Chief, particularly his account of the major operation necessary to remove a small foreign body from the upper lid of this famous man who ordinarily was very composed, dignified, and not addicted to profanity.

As for avocation, Dr. Fewell was a man's man, being interested in hunting, fishing, and outdoor sports, particularly tennis, a game that he evidently had sharpened while in California where he played with some outstanding players. He was an expert at poker and bridge.

Dr. Fewell will be missed not only by his many friends and patients, but also by numerous Graduate School students who will always feel indebted to him for the time and effort he gave them in this teaching.

Dr. Fewell is survived by his wife, Alice Urquhart; a daughter, Louise Motten, whose husband is Professor of History at Temple University; and two physician-sons, John William, now practicing medicine in Philadelphia; and Richard, practicing in Burlington, North Carolina.

In conclusion, I might use a phrase that Dr. Fewell may have mentioned in his early teaching days—*Requiescat in pace.*

Memoir of William Parks Belk 1889–1965*

By EDWARD ROSE, M.D.

WILLIAM PARKS BELK was born in the small community of Charleston, North Carolina, 31 July, 1889. He received his bachelor's degree in 1910 from the University of North Carolina where he was active in campus affairs and athletics. After two years in the medical school at that institution, he transferred to the University of Pennsylvania School of Medicine, where he graduated in 1914. During his internship at the Episcopal Hospital in Philadelphia, he developed the interest in clinical pathology which was to determine his subsequent career.

He served with the American Ambulance in a Paris hospital until the United States entered World War I in 1917. He then enlisted in the American Expeditionary Force and was assigned to the 17th Field Artillery of the Second Division with the rank of captain. He saw much action and received the Croix de Guerre with Palm for gallantry under fire. After the armistice he served with the United States Army of Occupation in the Rhineland until 1920.

Upon his return he became active in the teaching and practice of clinical pathology. He was appointed director of laboratories at the Bryn Mawr Hospital and was affiliated with the University of Pennsylvania School of Medicine. At various times he was instructor in clinical biochemistry, associate in clinical microscopy, associate in physiological chemistry and assistant professor of pathology in medicine.

After resigning from the staff of the Bryn Mawr Hospital in 1931, he operated a private clinical laboratory in Ardmore for several years. He then served as director of the laboratory of clinical pathology at the Episcopal Hospital until 1957 when he was appointed to a similar position at the Mercy-Douglass Hospital. After resigning this position because of ill health in 1964 he became affiliated with the Division of Laboratories of the Pennsylvania Department of Health until his death on 8 March, 1965.

He was elected a Fellow of The College of Physicians of Philadelphia on 12 May, 1930. He was a founding Fellow of the American College of Pathologists, a founding member and past president of the Pennsylvania Association of Clinical Pathologists, and also helped establish the Section on Clinical Pathology of the Philadelphia County Medical Society. He was a diplomate of the American Board of Pathology, a Fellow of the American College of Physicians, and a member of the American Society of Clinical Pathologists. For many years he served on the Board of Health of Lower Merion Township. He was a member of the Bryn Mawr Presbyterian Church. He belonged to the Delta Kappa Epsilon and Phi Chi fraternities. In 1922 he married Elizabeth Cassidy of Wilkes-Barre. They had no children.

His bibliography of some 30 papers reflects the breadth of his interest in pathological anatomy, technical aspects of laboratory medicine and blood transfusion. He investigated the lifespan of transfused erythrocytes long before isotope labelling was available. For many years he was actively interested in improving the quality of clinical laboratory procedures. In 1946, while chairman of the committee on laboratories of the Pennsylvania Medical

* Prepared and published at the request of the Council of The College of Physicians of Philadelphia.

Society, he initiated a survey of the accuracy of chemical analyses in clinical laboratories. This survey led to similar studies in other states and was instrumental in improving the quality of clinical laboratory work throughout the country. He vigorously advocated the role of the clinical pathologist as a specialist and consultant in his own right. He repeatedly demonstrated the courage of these convictions by actions which, though detrimental to his own self interest, he regarded as necessary for the maintenance of his principles.

I knew Dr. Belk as a friend, neighbor and professional colleague for more than forty years. The memory of his gentleness, his thoughtfulness, his quiet sense of humor, his kindness and instinctive courtesy will always remain. His earlier interest in golf was transferred in later life to regular early morning walks. He was an invariably charming and welcome companion, and an incessant reader with catholic tastes which reflected his scholarly and inquisitive mind. His physical courage was attested by his gallantry in military combat. His moral and spiritual qualities were demonstrated by the fortitude and uncomplaining patience with which he faced the long years of his wife's invalidism and the vicissitudes of health which beset him toward the end of his own life. His gentleness was not that of softness but rather that of strength.

In the death of William Belk the College has lost a scholarly and valued Fellow, his own discipline a dedicated and doughty champion, and, perhaps the greatest loss of all, many of us are bereft of a cherished friend.

Memoir of John Thompson Farrell, Jr. 1897–1965*

By MARIO A. CINQUINO, M.D.

DR. JOHN THOMPSON FARRELL, JR, Philadelphia Radiologist, died on April 30, 1965 at the age of sixty-seven. With his untimely death the College lost a distinguished member and friend.

Dr. Farrell was born on October 7, 1897, in Providence, Rhode Island, the son of John T. Farrell, M.D., and Louise Smith Farrell. He graduated from Hobart College in 1918 and from Jefferson Medical College in 1922. He served internships at Rhode Island Hospital, Providence, Rhode Island, and at White Haven Sanatorium, White Haven, Pennsylvania. Dr. Farrell married Miriam Ott in 1926. He is survived by two brothers and two sisters.

In 1925, after broad clinical training, Dr. Farrell returned to Jefferson and became associated with the late Willis F. Manges who was his preceptor in Radiology. After Dr. Manges' death in 1936, he established his own specialty practice. At Jefferson, Dr. Farrell rose through successive promotions to the rank of Professor of Roentgenology. From 1941 to 1948 he was radiologist to the Lankenau Hospital, Philadelphia. Up to the time of his death, he was Clinical Professor of Radiology at the Graduate School of Medicine of the University of Pennsylvania, Consultant in Radiology to the Mercy-Douglass Hospital, and engaged in private practice.

Dr. Farrell was always interested in organized medicine. He was elected a Fellow of The College of Physicians of Philadelphia in 1930. He became president of the Philadelphia County Medical Society in 1956, after serving on its Board of Directors for two years. He served on numerous committees of the Society and was a member of the House of Delegates since 1943. During his tenure of office greater cooperation was effected between the County Society and the city's Department of Public Health. The rapport and liaison which exists today between these two organizations is a tribute to him. He was also president of the Pennsylvania State Medical Society in 1958.

He was a Diplomate of the American Board of Radiology and a member of the American College of Radiology; American Roentgen Ray Society, Radiological Society of North America (Vice President, 1934), Philadelphia Roentgen Ray Society (President, 1930), Pennsylvania Radiological Society (President, 1944), American College of Physicians, Laennec Society, Medical Club of Philadelphia, Theta Delta Chi and Nu Sigma Nu.

Dr. Farrell was on the Board of Directors of Pennsylvania Blue Shield and Philadelphia Blue Cross. He was the author of numerous papers on the diagnostic and therapeutic phases of Roentgenology. His volume, *Roentgen Diagnosis of Diseases of the Gastrointestinal Tract,* was published by Charles C Thomas, Springfield, Illinois, in 1946.

The above facts simply show how active Dr. Farrell was, but do not adequately describe his personality. Because of his sincere love for people he made friends easily. He was honest in his work and in his association with his medical colleagues. Dr. Farrell's appreciation of right and wrong was clear and definite. He was easily upset by anything he considered to be unjust. Kindness, consideration and thoughtfulness were among his endearing

* Prepared and published at the request of the Council of The College of Physicians of Philadelphia.

traits. Few will forget his untiring efforts in the defense of the high principles and ethics of Radiology. Many will remember his determined labors for the improvement of hospital-radiologist contractual relationships.

In an article, "To Succeed", written for the *Philadelphia Inquirer* a few years ago, Dr. Farrell summarized the meaning of success—"In my opinion, to succeed is to get from one's work a sense of heart-felt satisfaction—not necessarily from the exact realization of early hopes or the acclaim of one's fellows, but from the feeling that with thoughtful industry and by playing the game fairly according to the rules, one has strived to reach that far star set in the sky of ambition".

Memoir of Albert Americo Martucci 1900–1965*

By ELMER J. ELIAS, M.D.

THE FOLLOWING portrayal of Dr. Albert A. Martucci is intended to reveal the life story of a Philadelphia physician dedicated to the practice of Physical Medicine and Rehabilitation and devoted to his family, colleagues and friends.

Who can forget "Al" with his twinkly eyes, smiling face, and hand extended to offer a greeting of warmth and assurance certain to make the recipient feel, "Here indeed is a friend"! These were qualities possessed by this learned physician and transmitted to each patient with whom he came in contact. They endeared him in the minds of countless persons who benefited from his knowledge and kindness.

Albert A. Martucci was born in Philadelphia on August 27, 1900, of proud Italian heritage. He attended the public schools and Temple University and graduated from the Temple University Medical School in 1927. He served his internship at the Abington Memorial Hospital. His interest in the disabled first found its outlet when he became an Assistant in Orthopedics at St. Christopher's Hospital for Children in 1929 and extended on there to 1949. However, during these years his quest for further knowledge of Physical Medicine was gratified by post-graduate study at the New York Polyclinic Hospital, in 1932, and at the University of Minnesota in 1940. With a surge of enthusiasm aimed to disseminate the knowledge of Physical Medicine, Dr. Martucci found opportunities to serve in various capacities at several medical schools and hospitals. He was appointed Associate Professor of Medicine at the Woman's Medical College in 1940; Associate Professor of Physical Medicine and Rehabilitation at the Graduate School of Medicine, University of Pennsylvania, in 1950; Clinical Professor of Physical Medicine and Rehabilitation at the Temple University School of Medicine, in 1952. In 1948 he became Chief of Physical Medicine and Rehabilitation at the Philadelphia General Hospital; his years of experience and the excellent results of original work developed in this specialty made him a respected authority, not only in Philadelphia, but throughout the country.

Tremendous drive and genuine desire to aid the handicapped resulted in additional committee appointments and honors bestowed on him both on a local and a national level. In 1946 he was appointed Consultant in Physical Medicine and Rehabilitation at the Veterans Hospitals at Philadelphia and Coatesville. From 1942–1958 he served as Chairman of the Commission of the Pennsylvania State Medical Society, and was also Chairman of its Coordinating Committee for the Handicapped from 1950–1958. He was a charter member of the American Academy of Physical Medicine and Rehabilitation in 1947. He was elected a Fellow of the Philadelphia Orthopedic Club in 1938; a Fellow of The College of Physicians of Philadelphia in 1954; a Fellow of the American College of Physicians in 1958. A member of the Philadelphia Rotary Club, he devoted his talents to its Committee on the Handicapped. In 1956 he was awarded the Presidential Citation for his work in promoting equal opportunity in

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employment for the physically handicapped.

Besides serving on the Professional and Advisory Boards of the United Cerebral Palsy Foundation of Pennsylvania, Philadelphia and Vicinity, he helped organize and set up diagnostic clinics for Cerebral Palsy in New Jersey, serving as Consultant to Clinics in Camden, Millville, Woodbury, and Riverside.

Recognition of his persistent and hard work over the years brought the following awards:

Certificate of Appreciation and Citation by the President, U.S. Selective Service, Member 1941–1945.

Meyer B. Strause Award for Outstanding Achievement in the field of Chronic Disease and Rehabilitation, Moss Rehabilitation Center, Philadelphia, April, 1960.

Man of the Week Award, Provident Tradesman Bank, Philadelphia, December, 1960.

Citation from the Graduate Club of Philadelphia for Accomplishments in the Field of Physical Medicine and Rehabilitation; also for work in Morocco, Aiding Paralyzed Victims of Adulterated Cooking Oil, February, 1961.

Community Service Award from the Chapel of the Four Chaplains, Philadelphia, in recognition of Outstanding Services to all people in the field of Physical Medicine and Rehabilitation, May, 1961.

Though dedicated to the teaching and practice of Physical Medicine and Rehabilitation, Dr. Martucci found time for his family, home and friends. His hospitality was extended to residents, students, colleagues and friends on many occasions in the congenial atmosphere of his home.

Margaret Martucci was the constant companion of her husband, whether at a meeting in Philadelphia or a distant point in the United States or in another country. During his one month tour of duty in Morocco, North Africa, as a consultant for Medico, in 1960, she served as his nurse-assistant in supervising the rehabilitation of paralyzed victims that numbered into the thousands.

At family reunions, daughter Paula with her husband, Dr. Robert Rodgers, and son, Dr. Albert, Jr., and his wife, Constance, and four grandchildren provided the atmosphere of greatest contentment for Al Martucci.

In 1962 a serious illness kept Dr. Martucci hospitalized for four weeks; after a short convalescence he was back at work with the same enthusiasm, but at a slower pace. He had a mission to accomplish and was determined to complete as much of it as possible.

On June 7, 1965, Dr. Albert A. Martucci was called to receive his final reward. His genial presence will linger long in our memories.

Report of the Secretary for the Year Ended December 28, 1965

		(Attendance)
Stated Scientific Meetings:		
January	The Forty-ninth Nathan Lewis Hatfield Lecture Carl A. Moyer, M.D.	147
February	The Seventy-seventh Thomas Dent Mütter Lecture Robert C. Mellors, M.D., Ph.D.	125
March	The Forty-fourth James M. Anders Lecture John R. Ellis, M.B.E., M.D., F.R.C.P.	72
April	The Eighty-ninth Mary Scott Newbold Lecture Professor Dirk Durrer, M.D.	96
May	At the Philadelphia County Medical Society. Presentation of the First Annual Kenneth E. Appel, M.D. Award to Robert E. Jones, M.D., Institute of the Pennsylvania Hospital, by Paul J. Poinsard, M.D. Presentation of Certificates to Physicians who have completed fifty years in the practice of medicine. Certificates awarded by Richard A. Kern, M.D., President, Pennsylvania Medical Society.	
October	The Sixth Hira S. Chouké Lecture Max Samter, M.D.	73
November	Joint Meeting with the Philadelphia County Medical Society. The Ninetieth Mary Scott Newbold Lecture Jacques Genest, M.D., F.R.C.P.(C), F.R.S.C.	95
December	The Twenty-fifth Alvarenga Lecture Harry F. Harlow, Ph.D.	85

	(Total Ballot)
Regular Business Meetings	
January 6, 1965	316
February 3, 1965	252
March 3, 1965	249
May 19, 1965	284
November 3, 1965	275
December 1, 1965	236
	(Ballot for Amendment)
May 19, 1965	277

The College of Physicians of Philadelphia awarded the Alvarenga Prize Award on July 14, 1965, to Harry F. Harlow, Ph.D. (Psychology), for his outstanding work on Social Deprivation in Monkeys.

	(Membership)
Sections of the College	
Ophthalmology	81
Otolaryngology	50 & 3 Honorary
Public Health, Preventive & Industrial Medicine	75
Medical History	134

Membership:

	Fellow	Non-Res.	Assoc.	Honorary		Hon. Assoc.	Total
				Foreign	U.S.		
December 29, 1964	1085	154	0	3	5	3	1250
Died during year	20	1		1			22
Resigned	8	1					9
Elected	50				1		51
Transferred from Resident to Non-Resident	−8	+8					
Transferred from Non-Resident to Resident	+1	−1					
Failed to qualify	0						
Forfeited	13	1					14
December 28, 1965	1087	158	0	2	6	3	1256
Life Membership							
New Type							
Under 70	22	7					
Over 70	27	7					
Old Type (Commutation dues)	7						
	56	14					
Dues Remitted							
Before 1965	44	10					
During 1965	5	4					
	49	14					
Annual Contributors as of December 28, 1965	982	130					

WILLIAM A. STEIGER, M.D.
Secretary

Report of the Treasurer for the Year Ended June 30, 1965

Assets

General Fund:			
Cash in bank and on hand			$ 29,915.97
Maintenance and Reserve Fund:			
Cash in bank		$ 1,391.42	
Investments		15,426.06	
			16,817.48
Joseph N. Pew, Jr., Memorial Loan Fund:			
Investments		21,502.19	
Notes receivable		13,500.00	
			35,002.19
Employee's Pension Plan:			
Investment with Insurance Company of North America			26,468.07
Trust Funds:			
Uninvested principal cash		37,518.62	
Uninvested income cash (restricted)		24,747.78	
Mortgage		30,375.00	
Real estate		158,905.33	
Bonds		401,938.25	
Preferred stocks		234,301.74	
Common stocks		861,105.50	
			1,748,892.22
Plant Fund:			
Land—16-25 South 22nd Street		95,000.00	
Building		1,420,747.93	
Furniture and fixtures		1.00	
Deposits on perpetual fire insurance policies		11,462.28	
			1,527,211.21
			$3,384,307.14

Funds

General Fund:			
Library general account		($ 5,530.59)	
Library medical documentation service		10,804.60	
Library special account		13,887.19	
Life membership account		1,340.00	
Reserve for contingencies—uninvested funds		190.02	
Greater Philadelphia Committee for Medical-Pharmaceutical Science		9,761.93	
Unexpended operating fund balances:			
Current operations—overexpended	($1,082.10)		
Committee on Interns and Residents	717.89		
President's room	525.00		
Books—over-expended	(1,020.39)		
Rare books	100.00		
Campaign expense	95.95		
Portrait	126.47		
		(537.18)	
			$ 29,915.97
Maintenance and Reserve Fund—principal			16,817.48
Joseph N. Pew, Jr., Memorial Loan Fund—principal			35,002.19
Employees' Pension Plan—principal			26,468.07

Trust Funds:			
Principal net worth			
Discretionary common trust fund	1,654,843.24		
Legal common trust fund	24,097.94		
Trust funds not pooled	14,828.26		
Fund for purchase of units in discretionary common trust fund	30,375.00	1,724,144.44	
Income net worth			
Discretionary common trust fund	21,204.30		
Legal common trust fund	1,215.78		
Trust fund not pooled	2,327.70	24,747.78	
			1,748,892.22
Plant Fund—principal net worth			1,527,211.21
			$3,384,307.14

NOTES: The various fund investments are shown at their recorded values, which values substantially represent cost.

GENERAL FUND

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

Year Ended June 30, 1965

Receipts:				
Income on investments, net of agents fees:				
Trust funds		$89,690.64		
Less:				
Amount transferred to income of the several restricted trust funds	$11,894.24			
Erlanger Garage expenses paid	5,202.50			
		17,096.74		
			$72,593.90	
Income from funds, principal of which is not administered by College		2,592.14		
Less, amount transferred to income of a restricted fund		467.55	2,124.59	
Interest on mortgage		1,430.14		
Income from other funds		2,649.10	4,079.24	$ 78,797.73
Contributions				
Fellow dues			87,705.13	
Life membership			2,725.00	
Use of hall and projector			3,357.00	
For Greater Philadelphia Committee for Medical-Pharmaceutical Science			25,500.00	119,287.13
Transfers from other funds:				
For reducing deficit in current operating account:				
Miscellaneous Contributions Fund			3,482.79	
Maintenance and Reserve Fund			23,766.62	
			27,249.41	
For covering deficit of Entertainment Committee:				
S. Weir Mitchell Entertainment Fund			778.30	28,027.71
Library:				
Contribution plan		21,093.38		
Photostats, fines, etc.		26,096.81	47,190.19	
Medical documentation service			40,192.38	
Special account contributions			16,525.00	103,907.57
Miscellaneous				2,728.68
Total receipts				332,748.82

Disbursements:			
Operating expenses:			
Hall Committee		$ 40,725.19	
Office of the Secretary		8,643.44	
Office of the Treasurer		11,314.73	
Pensions		14,159.69	
Campaign expenses		10.00	
Publication Committee		7,171.73	
Books		2,581.58	
Entertainment Committee		2,732.80	
College Collections Committee		3,884.92	
Library general:			
Salaries	$99,172.21		
Books, journals, supplies, etc.	54,820.32	153,992.53	
Medical documentation:			
Salaries	22,394.72		
Other expenses	6,993.06	29,387.78	
Library Special:			
Expenses		2,637.81	
Greater Philadelphia Committee for Medical-Pharmaceutical Science		20,979.74	
Net profit in Erlanger Garage account applied to deficit of July 1, 1964		9,665.00	
			$307,386.94
Excess of receipts over disbursements			24,861.88
Cash balance, November 10, 1964			5,054.09
Cash balance, June 30, 1965			$ 29,915.97

Statement of Cost of Investment Units Purchased in the Various Trust Funds by the Restricted Endowment Funds

July 2, 1964 to July 1, 1965

Discretionary Common Trust Fund:		
Balance, July 2, 1964		$698,175.37
Receipts:		
S. Weir Mitchell Associates journal fund	$18,810.66	
E. E. Montgomery Library Fund	2,000.00	
Wm. Zentmayer Book Fund	15,000.00	
Wm. Zentmayer Section on Ophthalmology	1,000.00	
Life Membership Fund	1,341.88	
Transfers from unit adjustment account:		
S. Weir Mitchell Associates journal fund	44.13	
Life Membership Fund	21.67	
	38,218.34	
Less: Retirement of Pension Reserve Fund units	13,955.12	
Less: Amounts insufficient to purchase one unit, credited to unit adjustment account	65.07	
		24,198.15
Balance, July 1, 1965		722,373.52
Legal Common Trust Fund:		
Balance, July 1, 1964 (no change during year)		23,500.00
Trust Funds Not Pooled:		
Balance, July 1, 1964 (no change during year)		14,974.56
Total restricted endowment funds, July 1, 1965		$760,848.08

STATEMENT OF COST OF INVESTMENT UNITS PURCHASED IN DISCRETIONARY COMMON TRUST FUND BY THE GENERAL ENDOWMENT FUND

July 2, 1964 to July 1, 1965

Balance, July 2, 1964		$ 428,715.68
Receipts:		
Entrance contributions	$ 2,750.00	
Voluntary contributions from Fellows, etc.	12,737.20	
Book of Remembrance	230.00	
Amortization of mortgage—13th and Locust Streets	2,250.00	
Estate of William Zentmayer	46,803.79	
	64,770.99	
Less: Amount insufficient to purchase one unit, credited to unit adjustment account	4.90	64,766.09
Balance, July 1, 1965		$ 493,481.77

BY THE COLLEGE EXTENSION FUND

July 2, 1964 to July 1, 1965

Balance, July 2, 1964		$ 3,960.71
Receipts:		
Voluntary contributions from Fellows	$190.00	
Income earned on invested principal	183.81	
Transfer from unit adjustment account	22.46	
	396.27	
Less: Amount insufficient to purchase one unit, credited to unit adjustment account	22.35	
		373.92
Balance, July 1, 1965		$ 4,334.63
Total of all restricted funds, July 1, 1965		$1,258,664.48

KENDALL A. ELSOM, M.D.
Treasurer

Annual Report on the Library*

Administrative

Give and Take. This year we relearned the basic lesson that it is easier to give things away than it is to secure a quid pro quo for services rendered and for responsibilities voluntarily shouldered. This is no less true when the potential donor and current recipient is the federal government. Many institutions are searching their corporate souls to see whether it is better to concentrate on the home front or to join the line of standees pleading for governmental support. Perhaps with no more hesitancy than the average, the library administration threw its whole hearted support behind the Health Sciences Library Assistance Act of 1965 in the hopes of finding a solution to the financial problems of a private institution with a long record of service to the public and to the government itself. The chronicle of these efforts and the critical self examination which accompanied them, forms the first section of this annual report.

Helping Hands. The willingness of Philadelphia area physicians and their friends to buttress efforts to secure national legislation to aid medical libraries was first demonstrated in the summer of 1964. Letters stimulated in part by this Library's Selected List of Publications, assured the Director of the National Library of Medicine of local interest. The response to this initial request was reported in the July/August and September issues of the Selected List. An even more enthusiastic response was provoked by the Feburary 1965 Selected List which announced the actual introduction of S.597 and H.R.3142 by Senator Lister Hill and Representative Oren Harris. At least 98 letters were written to Congressmen and to the White House.

Extra Efforts. In addition to the traditional letters to Congress, an exhibit was placed in the Lobby of the College, giving information on the proposed legislation. An article in support of the Act was written by Samuel X Radbill, M.D. for publication in *Philadelphia Medicine.* Dr. Radbill was also instrumental in securing the endorsement of the Philadelphia County Medical Society and the State Medical Society of Pennsylvania. Dr. Radbill also authored an article in the *Pennsylvania Medical Journal* describing the history and modern services of the College of Physicians Library. Congressmen were also apprised of resolutions approved by the Philadelphia Regional Group of the Medical Library Association and by the Philadelphia Regional Medical Library Committee.

Pitfall Avoided. One early threat to S.597 was the White House feeling that general library assistance provided in the President's omnibus education bill (S.600) was enough and that there was no need for special legislation tailored specifically for medical libraries. Correspondence with a Special Assistant to the President initiated by the Librarian and by many other interested parties was able to point out that (S.600) did not provide support for the many medical libraries which do not happen to be parts of institutions of higher learning. Fortunately White House attention could be drawn to the report of The President's Commission on Heart Disease, Cancer and Stroke where Recommendation 30. does not limit medical library support to institutions of higher learning. In May 1965 Administrative support was given to the legislation then carrying the title, Medical Library Assistance Act of 1965.

Philadelphia Solidarity Demonstrated. A most impressive demonstration of Philadelphia Medicine's statesmanship occurred on June 2, 1965 between sessions of the Medical Library Association convention. Martin M. Cummings, M.D., Director of the

* November 1, 1964–October 31, 1965.

National Library of Medicine, and Carl D. Douglass, PH.D., Chief, Research and Training Division, Extramural Programs, National Library of Medicine, accepted an invitation to attend a meeting of the Philadelphia Regional Medical Library Committee. The meeting was called to discuss ways in which Philadelphia medical libraries, in general, and the Library of the College of Physicians of Philadelphia, in particular, can best cooperate with the Extramural Program of the National Library of Medicine. The discussion was moderated by John Franklin Huber, M.D., PH.D., Chairman of the Philadelphia Regional Committee. Distinguished invited guests included: Robert M. Bucher, M.D., Dean, School of Medicine, Temple University; John H. Gibbon, Jr., M.D., President of The College of Physicians of Philadelphia; John C. Hetherston, Vice President for Coordinated Planning, University of Pennsylvania; Glen R. Leymaster, M.D., President and Dean, Woman's Medical College of Pennsylvania; Bruce V. MacFayden, M.D., Chairman, Library Committee, Hahnemann Medical College; Lysle H. Peterson, M.D., Professor of Physiology, Director of Bockus Research Institute, and Head of Computer Policy Committee, University of Pennsylvania; I. S. Ravdin, M.D., Vice President for Medical Affairs, University of Pennsylvania; and William A. Sodeman, M.D., Dean and Vice President for Medical Affairs, Jefferson Medical College and Chairman of the Philadelphia Medical Deans' Committee.

Dr. Cummings expressed his appreciation for the great quantity of letters from the Philadelphia area written in support of the Medical Library Assistance Act. He also indicated delight at the demonstration of community support evidenced by the medical school representation at the meeting. Drs. Bucher, Leymaster, MacFayden, and Sodeman indicated the dependence of their long range library planning upon a strong College of Physicians Library offering regional services. Dr. Gibbon reported the financial problems inherent in providing such a resource and the need for supplementary governmental support.

Dr. Douglass differentiated between regional medical libraries which might receive government aid and libraries which may be selected for decentralized output from MEDLARS tapes. Drs. Cummings and Douglass assured the local representative that the National Library of Medicine would take the initiative in suggesting the next moves to be taken by the regional groups and that the College of Physicians Library had been on all lists of proposed regional libraries.

Members of the host Philadelphia Regional Medical Library Committee present were Dr. Huber, Miss Jacqueline Bastille (Smith Kline & French); Mrs. Lucy F. Cooke (Hahnemann Medical College); Mrs. Ruth Y. Diamond (Temple University School of Medicine); Miss Ida J. Draeger (Woman's Medical College); Miss Frances R. Houston (University of Pennsylvania School of Medicine); Mrs. Helen Lake (Philadelphia General Hospital); Mr. Robert T. Lentz (Jefferson Medical College); and Samuel X Radbill, M.D., and Mr. Elliott H. Morse (College of Physicians of Philadelphia).

Denouement. The Health Sciences Library Assistance Act was signed into law on October 23rd but no funds were provided in the supplemental appropriation bill and funding was postponed for the next supplemental bill to be submitted by the President in January.

Fly in the Ointment. Rather than make our readers wait until next year for the latest chapter in this legislative case study, it must be added that when appropriations were made in January they did not provide direct support to regional libraries although other sections of the legislation provide help for which regional libraries and all others will be eligible. Needless to say this is disappointing after the regional library

concept was one of the prime motivating factors of the legislation and since our own supportive efforts were predicated primarily on that recognition. Doubly disappointing is the realization that selective appropriations for certain parts of legislation may have the effect of distorting the intent of Congress so clearly expressed by an almost unanimous vote for the original bill. However, if nothing else is learned from personal experience in the physiology of government, one learns patience and the virtues of persistently sweet reasonableness.

Why Not. A clearer understanding of the opposition to direct support now for regional libraries can be elicited from a careful reading of testimony presented to the Congressional committees considering the legislation. Since the Bureau of the Budget has a determining voice in the allocation of funds for specific sections of the bill, it is appropriate to examine the testimony of Mr. Phillip S. Hughes, Assistant Director for Legislative Reference on behalf of the Bureau of the Budget. A letter dated June 1st 1965, presented at the Senate hearings on September 14th 1965, contains the following pertinent passages.

"While the Bureau of the Budget recognizes the importance of the objectives of H.R. 3142, we note that there appears to be uncertainty as to the future course of development of scientific—including biomedical—libraries in view of the rapid advances being made in techniques for the indexing, storage, and retrieval of information. This has led us to the following conclusions:

"1. That a study should be undertaken of future biomedical library needs which takes full account of developing techniques for the improved handling of scientific information. The Office of Science and Technology has agreed to undertake such a study.

"2. That it would be prudent to defer beginning a program of medical library construction until 1967 in order to allow time for the completion of the above study and consideration of its implications on the facilities needs of medical libraries."

Optimists will take comfort from the fact that the door has not been firmly closed and that more information is being sought to produce valid judgements. Pessimists will recognize overtones of the philosophical dialogue between the extremists among the machine men who believe the computer will solve all information communication problems and the proponents of the traditional library which is the work horse now supplying the hard copy of medical literature. Unless sweet reasonableness prevails, we may burn our shoes before we learn to fly.

Philadelphia Regional Medical Library Committee. In addition to the meeting reported above, the Regional Committee met twice more during the present report year. In March, the Committee received a most interesting report from Dr. Lysle H. Peterson on plans for the Philadelphia City Science Center. He stressed the Center's interest in storage and retrieval of information in the interdisciplinary sciences such as biomedical engineering. The Center hopes to provide a base which will include engineering, linguistics, and information science. Dr. Peterson visualizes a specialized information center for medical and life sciences with emphasis on introduction of the benefits of machines.

The Regional Committee met again in April to explore ways in which the regional services of the College Library might be increased. Among the suggestions for expanded services were the following: facsimile transmission of library material from the College Library, regional distribution of bibliographic information from MEDLARS tapes, cooperative storage of less used materials, reduction of costs of photoduplication of library materials, shortening of time required for binding, strengthening of reference services through increased personnel and augmented reference tools, telephone reference service based at the College Library, and increased coverage of journals included in *Index Medicus.*

The Crystal Ball. The Library Commit-

tee and the Library Administration have allowed the prospect of federal support to stimulate the formulation of long-range objectives for optimum development of the Library's potential for service, training, and research. The following nine point program was discussed and approved at the October meeting of the Library Committee.

1. To improve and expand the present methods and policy for acquiring books, journals, audio-visual equipment, duplicating services, etc.

2. To develop a training program, we should explore affiliation with the School of Library Science at Drexel and estimate needs for space, personnel, and program materials.

3. To rehabilitate and expand existing facilities including more book stack space, staff working area, air conditioning and humidity control, and staff facilities including an adequate staff lounge.

4. To strengthen our supplementation of dental, pharmaceutical, biochemical, veterinary medical, social science and paramedical holdings of other libraries in the region.

5. To investigate advances in new tools and library methods. A new department should be established to explore machine techniques and their possible application to such library procedures as the storage, retrieval, and dissemination of health science information, as well as maintenance of library records.

6. To expand the College Library's capacity as a regional medical library by instituting a facsimile transmission network between the College Library and local medical libraries and to establish a facsimile transmission link with the National Library of Medicine.

7. To consider the purchase of additional property if it is suggested by space requirements for training programs, computer and machine facilities, and transmission and duplicating equipment.

8. Support biomedical publications such as the *Transactions & Studies of the College, Fugitive Leaves*, a catalog of the Library's manuscript collections, publications of an historical and teaching center, and abstracting and bibliographical bulletins.

9. To augment and increase existing services to the community by providing: a regional messenger service, a subsidized photoduplication service, subsidized bibliographic services, expanded telephone and teletype reference services, deposit library service for smaller hospitals, and advisory assistance to newly established medical libraries in the area.

Return to the Mundane. Following the exhilaration of plans unhampered by limitations of budget, space, and personnel, the following account of library life last year should have a sobering effect.

The College Library in 1964–65

Fiscal Year. The first new style (July–June) fiscal year ended on June 30, 1965, in the course of the current administration report year (November–October). The Library Administration working figures have not been reconciled with the auditor's statements which appear in somewhat different categories. However, for purposes of broad comparison, it is pertinent to note that library expenditures of about $191,000 exceeded income of $185,000. The need for increased extramural support is clear. Income from endowments and current appropriation constitutes about one half of the library income while Fellows' use of the College continues to represent about ten percent of total library use. Outside support provides about twelve percent of library income.

Friends of the Library. As the current report year was closing, the President of the College, aided by a Women's Committee, was formulating plans for a Friends of the College of Physicians Library group. The Friends group will provide an opportunity to the laity as the S. Weir Mitchell

Associates does for the profession, to offer individual support to the College Library. Sustaining memberships will be $100 per year or more. Individual memberships are available at $10.00 per year. Prospects will be sent an illustrated brochure which was published through the courtesy of the W. B. Saunders Co.

Journal Acquisition Program. Funds provided by many of the Library's registered commercial borrowers, were used to survey the Library's list of currently received journals and to initiate efforts to increase the coverage of journals included in *Index Medicus*. A study of the lists of journals indexed, published in the January and subsequent 1965 issues of *Index Medicus* pinpointed 1,238 serials not currently received by the College Library. Included in this total were 54 journals which are only selectively indexed and 441 journals which are only indexed for review articles. These titles will be given a very low priority in any acquisition program. Another 160 titles are no longer indexed. Secondary emphasis has been given to certain journals in subject fields peripheral to the Library's primary collecting obligation such as: veterinary medicine (23); biological sciences (32); dental medicine (53); collateral sciences (14) and nursing (4). In each case there are other Philadelphia libraries with primary interest in these fields.

Highest priority was given to 229 titles, in strictly medical areas, in languages other than Slavic and Oriental. Journals in these languages, numbering 91 and 45 respectively, will be considered in connection with the list of journals published in the January 1966 issue of *Index Medicus*. For the remaining journals, subscriptions were entered or letters were written soliciting gifts or proposing exchanges. Later in the year, subscriptions were entered for journals which had not responded to gift and exchange requests. The full impact of this program is not reflected in the increase in the number of currently received journals to 3,210 this year from 3,121 last year. Overseas correspondence and placement of subscriptions with importing agencies is a tedious process.

Concurrently the Library scrutinized journals received which are not covered by *Index Medicus*. Twenty-five subscriptions were cancelled out of a list of 145 titles not in *Index Medicus*. Retained titles usually represented fields of special College Library interest such as ophthalmology, dermatology, pediatrics and medical history where endowed funds and long established policies have developed subject strengths.

Currently Received Periodicals Display. Periodical Room shelving permits the storage of current issues of less than one third of the journals coming into the Library. The larger portion of each day's receipts is shelved in the stacks beyond the surveillance of most of the Library's users. To mitigate the effects of this limitation, a "current display" table has been provided in the Periodicals Room. All issues received are displayed on this table for twenty-four hours before shelving. Visitors may put reserves on journals displayed and may withdraw them at the end of the display period. An encouraging number of Library visitors are availing themselves of this opportunity to scan this accretion.

Library discards. During the summer months, the Library embarked on a weeding program in the section of stacks housing reports of state and city governmental units. Titles which were represented by widely scattered issues or which originated in geographically remote areas were examined critically. Additions had not been made to the majority of these files since the early nineteen twenties and in most cases did not precede the eighteen nineties. Much material was from subject fields as little related to primary collecting interest as state departments of agriculture reports.

All medical material of local geographical interest was retained. Reports from more remote areas were offered to li-

braries which recognize regional responsibilities in each section of the country. Letters were sent to thirty different medical and historical libraries together with cards for the material being offered. Replies were received from almost all correspondents and a gratifying portion of the material augmented existing files in more logical depositories.

Although a considerable amount of effort was expended, much shelf space was gained and material of parochial interest has been transferred to libraries where its usefulness is enhanced.

Pension Plan. Members of the Library Staff were especially cheered by the interest demonstrated by the College by a major revision of the provisions for pensions for College employees. Included in this enlargement of benefits was an employer paid life insurance policy for eligible employees.

S. Weir Mitchell Associates. Although the initial growth rate has slowed, there is a continuing interest in this endowment program which provides a unique perpetual demonstration of a Fellow's concern for the strength of the College Library. Endowments of $1,000 have been received or pledged for 137 journals. The previous annual report indicated 125 endowments. Lists of journals available for endowment will be supplied by the Library or by Dr. George I. Blumstein, the energetic chairman of this Committee.

Host City. Library associations, attracted in part by the Bicentennial observance of the Medical School of the University of Pennsylvania, selected Philadelphia as the city of choice for their 1965 conventions. Members of the College Library staff were pleased to participate in the plans and sessions of the Catholic Library Association, the Medical Library Association, and the Special Libraries Association.

Equipment. Air conditioning of the library workroom and the acquisition of machinery which promises heat relief in the reading rooms next summer was warmly welcomed by the Library staff. Special thanks went to Dr. John P. Hubbard, who donated most of the equipment, and to Mr. Theodore J. Kolodziejski, the Superintendent, who supplied the technical competence and physical strength to transport the machinery to the College and to reassemble it.

A new mimeograph machine with fewer idiosyncrasies now permits a larger number of staff members to participate in multicopying operations.

Ten or More. A cogent testimony to the Library's regional activity is the November 1965 Report of the Library Administration. This list of institutions which borrowed "Ten or More" volumes during the current report year includes 110 different organizations. Seventy-six of these institutions have increased their use since the previous year's study. There are seven libraries which did not appear on the 1964 list.

The total number of volumes borrowed by the "Ten or More" group rose to 21,555 from 20,725 last year. This select group constitutes 30.3 percent of the total of 338 libraries which borrowed 21,736 volumes during the year. Loans were made to libraries in 32 different states, three Canadian provinces, and to a library in Paris, France.

Among these "Ten or More" institutional borrowers are nine federal, six state, and two municipal agencies and one organization which operates almost entirely on government grants. Twenty-seven of the libraries are located outside of Pennsylvania.

By type of library, we find 31 commercial organizations, 28 hospitals, 24 varied non-profit institutions, 17 governmental agencies, and 11 medical schools. Perhaps most encouraging is the fact that 65 of these organizations are contributing to the support of the College Library. Federal restrictions account for the fact that governmen-

tal libraries constitute the largest group of non-contributing institutions. Sharing of this report with the National Library of Medicine brought a response indicating the Director's pleasure and sympathy for the hard data on community use of the College of Physicians of Philadelphia Library. We were assured that this information will be added to the documentation of our case for support. Copies of this report will be sent to any other interested persons on request.

Personnel. The present report year and developments since the close of the formal year have seen major changes in the Reference/Circulation Department. Mrs. Edis Hall, Mrs. Judith Overmier, and Mrs. Grace Wozniak all worked in this Department on part-time bases while studying in the Graduate School of Library Science at Drexel Institute. The completion of the course of study, intensification of scholastic endeavor, or husband's transfer to another city deprived the College of the services of all three of these assistants. A new part-time assistant was found in the person of Mrs. Rosayne Tumilowicz, another Drexel student, who joined the staff in March 1965. Two part-time jobs were combined to form a full time position which was happily filled by the appointment of Mrs. Julia O'Malley in August. Following the close of the annual report year, Miss Nancy Whitten resigned to accept the position as Administrative Head of the Historical Collection at the University of California, San Francisco Medical Center Library. A miracle of coincidence brought Mrs. Joyce S. Mingledorff to Philadelphia at the proper time to permit her appointment as Head of the Reference/Circulation Department to fill this vacancy. Mrs. Mingledorff served as Assistant Librarian in the School of Dentistry at Emory University before her husband's appointment to the Faculty of the Dental School at Temple University brought her to Philadelphia. She holds degrees from Huntingdon College and Emory University.

The Assistantship, in the Processing Dept., which is responsible for photoduplication, bookkeeping and other varied duties, was held successively by Miss Ida Stuber, Mrs. Nadeen Kaufman, Miss Barbara Appell and the present incumbent, Mrs. Margaret Henry, who served previously as a library page. The newly created assistantship with primary responsibility for typing is presently held by Mrs. Theresa Perretta, who replaced Mrs. Pamela Salkeld.

The Serials Department lost the services of a devoted staff member at the end of 1965 when Miss Dorothy Minton accepted the position of Librarian at the North American Publishing Co. This position was filled by Mrs. Doris Bridgman who had been a member of the staff of the Penniman Library at the University of Pennsylvania. Mrs. Charna Axelrod, who carried a part-time schedule in the Serials Department, discontinued her work to devote full time to studies and domesticity. Miss Myrna Fisher, a student at Drexel, has taken her place. Miss Barbara Maurer, also a Drexel student, continues the special Journal Acquisition Program, which was begun by Miss Nuha Shaath before her return to her native Egypt. Miss Gayle Donahower was employed in September to provide evening and Saturday relief in this department.

Newcomers to the Paging Staff this year are Terry Fox, Juneann Kasperowicz, Gloria Culler, Josepha Sereda, and Daniel Kelly.

The following individuals, who are no longer on the Library staff, served as Library Pages during the report year; Sandra Martin, Millicent Quammen, Thomas Summers, Geza Szarka, Millicent Lucas, and Augustus Young.

Professional Staff Activity. The convocation of the 64th Annual Meeting of the Medical Library Association in Philadelphia in 1965 gave many staff members an

opportunity to participate. Mrs. Kathryn E. Miragliotta was a member of the Registration Committee, Miss Muriel Zeldis served on the Program and Hospitality Committees, Miss Nancy Whitten was on the Publicity Committee and she prepared an article on Philadelphia medical libraries for publication in the *Bulletin of the Medical Library Association* as part of the advance publicity. Miss Whitten also served as Co-Chairman of the Meals Committee. Mr. Elliott H. Morse was the Convention Chairman. Mrs. Bernice Odom welcomed the convention to Philadelphia in her capacity as Chairman of the Philadelphia Regional Group of the Medical Library Association, the host organization. Especially gratifying was the Convention's designation of Dr. W. B. McDaniel as its Honorary Chairman. Miss Muriel Zeldis serves as a member of the Program Committee of the Philadelphia Regional Group of the Medical Library Association.

National assignments were accepted in the Medical Library Association by Miss Nancy Whitten on the Membership Committee and by Mr. Morse on the Committee on Federal Relations and on the MLA/NLM Liaison Committee.

Benefactors. A list of donors of books and other library materials appears in the statistical section of this report.

The Library acknowledges its gratitude to the following institutions which have shared the operational costs of the College Library.

NON-PROFIT INSTITUTIONS

Albert Einstein Medical Center, Medical Staff
Bryn Mawr Hospital Medical Staff
Chestnut Hill Hospital
Elwyn School
Episcopal Hospital
Fels Research Institute
Fitzgerald-Mercy Hospital
Germantown Dispensary and Hospital
Graduate School of Medicine of the University of Pennsylvania
Hahnemann Medical College
Harrisburg Hospital
Institute for Cancer Research
Jefferson Medical College
Lankenau Hospital
Misericordia Hospital
New Jersey College of Medicine and Dentistry
Arthur P. Noyes Foundation
Philadelphia General Hospital
Sacred Heart Hospital, Allentown
Saint Agnes Hospital
Temple University School of Medicine
U.S. Naval Hospital Staff, Philadelphia
University of Pennsylvania School of Medicine
University of Pittsburgh School of Medicine
Walson Army Hospital Staff
Woman's Medical College of Pennsylvania

COMMERCIAL INSTITUTIONS

Air-Shields, Inc.
Atlas Chemical Industries, Inc.
Auerbach Electronics Corp.
Baltimore Biological Laboratories
James E. Beasley, Esq., Attorney
Bell Telephone Company
Bernstein, Bernstein, Harris & Kessler
Borden Chemical Company, Research Laboratory
Campbell Soup Company
Cohen & Verlin, Attorneys
Council for Tobacco Research
Dechert, Price, and Rhoads
Dilworth, Paxson, Kalish, Kohn & Dilks
Duane, Morris, and Hecksher
E. I. du Pont de Nemours, Haskell Laboratory
E. I. du Pont de Nemours, Lavoisier Laboratory
E. I. du Pont de Nemours, Stine Laboratory
FMC Corp.-American Viscose Division
Frank C. Farnham Company
Freedman, Borowsky and Lorry
General Electric Co., Missile & Space Division
General Technical Services, Inc.
Hercules Powder Company
Institute for Scientific Information
Kisselman, Devine, Deighan & Montano
LaWall & Harrison Research Laboratories, Inc.
Lederle Laboratories (American Cyanamid Co.)
Lemmon Pharmacal Company
Lewis & Gilman, Inc.
MacAndrews & Forbes Company
McNeil Laboratories
Mead Johnson & Company
Merck, Sharp & Dohme, Rahway
Merck, Sharp & Dohme, West Point
Mulford Colloid Laboratories
National Drug Company
Norwich Pharmacal Company
Ortho Research Foundation
Pennsalt Chemical Corporation
Pennsylvania Railroad Company

Personal Products Company
Chas. Pfizer & Company
Philco Corporation
Quaker Chemical Corp.
Radio Corporation of America
Ransdell, & Buckly & Co., Inc.
Richter, Lord, Toll & Cavanaugh
Rittenhouse Book Store
Rohm & Haas Company
William H. Rorer, Inc.
Samson Laboratories
Schering Corporation
Schnader, Harrison, Seagal & Lewis
Smith, Kline & French Laboratories
Socony Mobil Oil Company, Inc.
Squibb Institute for Medical Research
Sun Oil Company
Arthur H. Thomas & Company
Ted Thomas Associates, Inc.
Wallace Laboratories
Worthington Biochemical Corporation
Wyeth Laboratories

E.H.M.

Historical

As was noted in last year's report (with an accompanying flourish of trumpets), Mrs. Lisabeth M. Holloway took over the duties of Cataloguer of Historical Materials on 16 Sept. 1964, which was too late in the report-year for a meaningful presentation of her initial activities. Now, at the close of her first full report-year, it must be said at the outset that she has given continuous occasion for further trumpet-flourishes. While her first annual report, which follows, may seem, to those of us on the same set, to do but meagre justice to the scope and depth of her activities, and those of her assistant, Mrs. Betty Voigt, it may yet serve to indicate why, not long after the close of this report-year, Mrs. Holloway's professional title was amended, by the Library Committee, so as to read: Associate Curator, and Cataloguer of Historical Materials.

Report of the Historical Cataloguer:

Items Catalogued

Books added to the collection (including early works and current works on the history of medicine)	218
Pamphlets	478
Pictures, documents and manuscripts	344
Books and pamphlets recatalogued (because of missing cards, erroneous entries, or misleading location symbols)	371
Total	1,411
Cards typed (including 1,964 Xeroxed cards)	8,953

Special Activities

1) Supervision of continuing housekeeping activities in the Cage. Since September, the Historical Collections have had half-time paging service, which has been devoted to cleaning and shifting of books in the Cage; reading and rearranging of shelves in the Gross Room; cleaning and treatment of leather bindings; and (3 hours a week) searching and checking of pamphlets from the College's uncatalogued collections, preparatory to cataloguing.

2) Maintenance and revision of the Portrait catalogue. Since the fall of 1964, responsibility for this file has rested with the Historical Cataloguer. This file represents a partial index to journals past and present, which has proved of service in obtaining biographical data—as well as portraits—for persons not readily discoverable otherwise. Extensive consolidation of entries and refiling continues to be necessary; this work is now principally the duty of the typist for this Department, Mrs. Betty Voigt, whose interest and attention have made this catalogue substantially more useful.

In December, 1964, Dr. Samuel B. Sturgis presented us with a valuable card index to the Sturgis Collection, in whose 100-plus portfolios he has arranged and preserved the great bulk of the College's unframed prints and photographs. We are much indebted to him, not only for his original work of physical preservation and organization, but also for this index, by which these important materials may be readily located.

3) Sale of duplicates from the Historical Collections. Our first list, comprising some 62 items priced for us by Mrs. Joanna

Grimes of the Old Hickory Bookshop, was distributed in the fall to Fellows of the College, medical libraries, and other interested persons and institutions. Over 80 percent of these items have been sold (many being requested twice over) at a gross of $548 (including a very few substitutions for items already sold). Two university libraries each bought over $100 worth, and it may be interesting to note that the University of Melbourne, Australia, ordered 12 items.

L. M. Holloway
Associate Curator and Cataloguer of Historical Materials.

Some Memorable Acquisitions:

Amatus, Joannes Carolus. Fructus medicinae, ex variis Galeni locis decerpti. Lyon, 1623. (Juan Carlos Amat was physician to the famous monastery of Monserrat, in Spain. According to Palau, this work—exact formulae of simples drawn from Galen, for a long list of diseases—had six or more printings in Spain in the 17th c., but our French edition is the only one we have found listed elsewhere, and that only once (Wellcome).

Caelius, Antonius. Introductio universalis ad medicam facultatem . . . Messina, 1618. (Though it is listed in the 17th century bibliographies by van der Linden, this 214-p. work evidently became so rare thereafter as to escape the attention of most of the later bibliographers.)

Duverney, Joseph Guichard (1648–1730). Oeuvres anatomiques. 2 vols. Paris, 1761. (A highly esteemed collection of works by the French writer who is credited with being the first to give a scientific account of the structure, function, and diseases of the ear.)

Fuchs, Samuel (1588–1630). Metoposcopia & ophthalmoscopia. Strassburg, 1615. (An interesting, illustrated, treatise on physiognomy and the estimation of character by the eyes.)

Gilibert, Jean-Emmanuel (1741–1814). L'anarchie médicinale, ou la médecine considerée comme nuisible à la société. 3v in 1. Neuchâtel, 1772. (A monumental attack on medical charlatans. This effects an entrée into our catalogue for a Montpellier medical graduate who was the author, editor, or translator of several highly esteemed publications.)

Koch, Robert (1843–1910). L'Etiologie de la Tuberculose . . . Berlin, Juillet 1883. (A 601-p. manuscript French translation, in a remarkably legible hand, of Koch's *Die Aetiologie der Tuberkulose*, the second of his classic works bearing that title and which was published in *Mittheilungen aus dem kaiserlichen Gesundheitsamte*, 2. Bd., 1–88, Berlin, 1884 (copy in the library). This manuscript seems to be the only French version of the work on record. The 1883 date on its title-page—ante-dating the date of publication of the German original—suggests a possibly rewarding line of research for some scholar.)

Zimara, Marco Antonio (1470–?1532). Antrum magico-medicum. 2 vols in 1. Frankfurt, 1625–1626. (Thorndike, in his *History of magic and experimental science*, devotes several pages (vol. 6, pp. 599–602) to this rather enigmatic author and the works, including this one, attributed to him.)

The Bicentennial Year. The year-long celebration of the founding of the School of Medicine of the University of Pennsylvania—"The Bicentennial of Medical Education in the United States", to give it its official running-head—inevitably found the library's historical collections rendering many types of related service throughout the year. Among the Senior Founders of the College in 1787, it will be remembered, were John Morgan, William Shippen, Jr, Benjamin Rush, and Adam Kuhn, who comprised the entire faculty of the School of Medicine at that time, and who, with

many of their distinguished successors, established a warm relationship between the School and the College that in the course of human events has naturally led to deposit in the College library of much primary material bearing on the history of the School of Medicine. This was drawn on freely, of course, by, among others, George W. Corner, M.D., for his bicentennial history of the School; by Whitfield J. Bell, Jr., PH.D., for his biography of John Morgan; and by Daniel M. Albert, M.D., and Harold G. Scheie, M.D., for their history of the School's Department of Ophthalmology.

The Historical Department of the library was instrumental in obtaining English translations of Morgan's and Rush's Edinburgh theses (based on the Library's copies of them, and subsequently published, revised and edited, in the College's *Transactions & Studies* during the bicentennial year). It joined with other departments of the College in providing considerable material for the Philadelphia Museum of Art's bicentennial-related exhibit entitled "The Art of Philadelphia Medicine".

Fugitive Leaves. There were six issues of the *Leaves* during the report-year, two fewer than in the report-year immediately preceding. N.s., Nos 73–75 concluded the excerpts from Nathan Lewis Hatfield's notes on lectures by members of the Jefferson Medical College's first faculty. No. 76 offered a Table of Contents of, and Index to, Nos 51–75. No. 77 reproduced, from a manuscript in the library, the 1806 Constitution of an only slightly recorded medical society, the American Aesculapean Society, of New York City. No. 78 attempted to identify the pseudonymous "Cato" who contributed a series of "Sketches of Eminent Living Physicians" to the *Boston Medical & Surgical Journal* around the middle of the 19th century; the attempt was, happily, judged successful by all correspondents heard from. The compliment of reprintings from two of the earlier *Leaves* belatedly came to our attention during the year: the journal *Scientiarum Historia*, published at Antwerp, in Dutch, offered, in 1963, a translation of No. 55, on the very rare Antwerp, 1512, edition of the Ketham *Fasciculus Medicinae*, a copy of which had recently been found and identified in our library; and, in October, 1964, *Guy's Hospital Gazette* reprinted, from No. 70, Dr. A. P. C. Ashhurst's entertaining account of his visit to the crypt at Guy's.

Exhibits. The practically continuous series of, often contiguous, annual meetings held here in tribute to the bicentennial precluded any attempt to meet all of the opportunities offered for specialized exhibits. Aside from a recurrent all-purpose exhibit, displaying some of the library's rarest treasures in various categories, special exhibits were prepared for the 50th anniversary meeting of the Philadelphia Orthopedic Society; in honor of the Lister centenary; for the meeting of the International Society of Surgery, and tangential societies; and, as usual, for the meetings of the College's Section on Medical History. Ten original drawings by the Fabers (Herman, and his sons, Ludwig and Erwin), from the Sturgis Collection, were loaned for exhibit at the Benjamin Franklin Hotel during the annual meeting of the Association of Medical Illustrators.

Extra-mural. The Curator served as chairman of the Program Committee of the American Association for the History of Medicine, as a member of its Committee on Arrangements for the annual meeting, held in Philadelphia, and completed his term as a member of its Council. He delivered the after-dinner address at the annual dinner of the Biological Sciences Division of the Special Libraries Council; and gave brief historical talks before several medical-student, and library, groups meeting in the College. He contributed the Historical Introduction to the "Bibliography of the History of Medicine of the United States and Canada, 1939–1960", edited by Gene-

vieve Miller (Baltimore, The Johns Hopkins Press, cop. 1964).

W.B.McD., 2d

Medical Documentation Service

In the earlier years of the Medical Documentation Service, the youth, one might say, growth, in terms of new ventures undertaken, was more dramatic and hence more amenable to interesting report. Now in relative maturity we can record only continued performance of old ventures.

Thus in the report year under review (and, as usual, comparable data for the previous year are given in parentheses after 1964–1965 figures) we reported a total of 4574 (4206) references on an average number of 26 (25) subjects. The income from this portion of our activity was substantially the same as last year.

The number of abstracts prepared was 775 (667) and the income was considerably more than the previous year.

We made 276 (192) literature searches and our income from this was $5,518. ($3,277.). Translation income was increased slightly—$9,211. ($7,171.).

The staff has remained faithful and consistently efficient. Jean Carr continues as our dependable Executive Secretary, Patricia E. Roddy as our capable part-time typist. Paul E. Walter resigned in mid-1965 and we had the services of George P. Gillen, skilled in Russian and German and a student at Temple University School of Medicine, during the summer. Barbara Flood, a graduate of Wellesley College and a former graduate student at Columbia University, now studying at Drexel Institute of Technology, joined the staff in September. The conscientious work of these persons and of our outside translators, typists and abstractors makes it possible for us to operate.

Three especial sources of satisfaction should be pointed out. *Birth Defects, Abstracts of Selected Articles,* for whose editorial matter we are entirely responsible, has increased in paid subscribers from 1257 in 1964 to 2190 in late 1965. In mid-1965 we received approval of our application to the NIH for a grant to enable us to publish *Influenza, An Annotated Bibliography.* The *fiscal* year (July 1, 1964 through June 30, 1965) showed an excess of income over expenditure. In the years 1958–1965 the operations of the Medical Documentation Service have resulted in a reduction of about $31,000. in the amounts the College has been required to appropriate for library operation.

W.L.B.

STATISTICAL SUMMARY*

Inventory

	1965		*1964*	
Accessioned items:[1]				
Incunabula[2]	421		421	
Manuscripts and typescripts	1,294		1,291	
General	227,061		221,914	
Accessioned pamphlets	6,688		6,036	
		235,464[3]		229,662

* November 1, 1964–October 31, 1965.

[1] Accessioned items in this library comprise the total number of bound volumes and such unbound pamphlets as have been cataloged as separate bibliographical units regardless of their size.

There remain many thousands of unaccessioned pamphlets awaiting accessioning and cataloging. A true quantitative and qualitative picture of the library's holdings cannot be presented until this wealth of neglected material has been processed and duly registered in our 'accessioned' count.

[2] The Library owns 423 incunabula, but there are two cases of two bound together, reducing the number of accessioned items.

[3] Included in this figure are the following collections which are on permanent deposit in the Library: Gross Library, 3,976 accessioned items; Parry Library of the Obstetrical Society of Philadelphia, 217; Mütter Museum, 200 (Mütter Museum books may not be removed from the College building.

Unaccessioned items:[1]

Reports	28,814	28,806	
Theses	61,871	61,436	
Pamphlets and reprints	229,396[4]	231,568	
	320,081[4]		321,810

Accessioned Acquisitions:

1965: 5,802 volumes (2,692 by purchase; 2,603 by gift; 507 by exchange). (Books: 1,600; Periodicals: 3,550; Pamphlets: 652).

1964: 6,005 volumes (2,974 by purchase; 2,463 by gift; 568 by exchange). (Books: 1,475; Periodicals: 3,975; Pamphlets: 555).

Non-accessioned acquisitions:[5]

1965: 468 items (Reports, 8; Theses, 435; Miscellaneous, 25).

1964: 385 items (Reports, 1; Theses, 315; Miscellaneous, 69).

Currently Received Serials

	Subscription	*Gift*	*Exchange*	*Tota*
U.S.A.	446	487	62	995
Western European Continent	822	103	138	1063
Eastern European Continent	148	67	59	274
United Kingdom and Eire	143	36	28	207
Asia (including Japan)	59	82	87	228
Latin America and West Indies	47	90	86	223
International	77	11	—	88
Canada	14	22	7	43
Pacific (including Australasia)	5	19	16	40
Africa	3	14	20	37
United Nations	12	—	—	12
Grand Total 1965	1776	931	503	3210
Grand Total 1964	1667	959	495	3121

New Titles: A total of 178 new serial titles was added in 1964/65.

Separate issues received, checked in the Kardex record and shelved totaled 23,807.

Readers' Use of the Library

Library hours. The Library was open, during the academic year, from 9:00 to 9:30 on Mondays and Wednesdays, from 9:00 to 5:00 on other weekdays. During June, July, August, and until the first Monday after Labor Day, the Library was open from 1:00 to 9:00 on Tuesdays and from 9:00 to 5:00 on other weekdays, except Saturdays, when it was closed. The following legal holidays were observed: Thanksgiving, Christmas, New Year's, Memorial, Independence, and Labor Days.

Visitors:

	Reading Room	*Periodicals Room*	*Total*
1965	10,240	3 392	13,632
1964	10,934	3,729	14,663

Circulation:

	Intra-mural[6]	*Extra-mural*	*Books*	*Journals*	*Total*
1965	34,325	33,025	12,153	55,197[7]	67,350
1964	32,132	33,253	11,715	53,670[8]	65,385

[4] Declines in these figures result from the weeding project described above in this report.

[5] As usual, not all the pamphlets, theses, and numbers of various journals listed as received have been checked for keeping or discard at the close of the Library year.

[6] The number of volumes "consulted in the library" includes only those supplied on demand. Readers have access to the bound volumes of periodicals and reference works kept on the shelves in the Reading Room; the Fellows, and occasionally others, by special permission, have access to the book stacks. There are, therefore, many volumes consulted of which no accurate record can be kept.

[7] This figure includes 4,853 unbound current journal issues circulated from the Periodicals Room.

[8] This figure includes 6,264 unbound current journal issues circulated from the Periodicals Room.

Interlibrary loans: The Library sent 21,736 (1964: 19,454) volumes on interlibrary loan to 338 (1964: 283) libraries in 32 (1964: 30) states, Canada (Ont., B.C., Saskat.) and Paris, France, and borrowed xx (1964: 17) volumes from xx (1964: 3) libraries.

Photoduplications: 109,971 pages were photocopied on request (1964: 121,935).

Donations

The donors for the past year number 85 (1964: 77). The library is indebted for large gifts of books, pamphlets and unbound periodicals to the following donors: American College of Physicians; Dr. S. Bellet; Biological Abstracts, Chestnut Hill Hospital, Children's Hospital; Dr. D. A. Cooper; Free Library of Philadelphia; Mrs. M. B. Gellman; Grand View Hospital; Drs. J. H. Hafkenschiel, Jr., W. E. Holt, K. M. Houser, R. A. Kern; Lea & Febiger, Ramsdell, Buckly & Co., Merck Sharp & Dohme, National Foundation, Penn Mutual Life Insurance Co.; Drs. S. X Radbill, J. B. Rudolphy; Saint Agnes Hospital, Smith Kline & French Laboratories, Temple Medical School Library, Wallace Laboratories; Dr. W. W. Wilson; Wistar Institute; Dr. I. J. Wolman; Woman's Medical College Hospital, and Wyeth Laboratories.

Various publishing houses, among the large group of corporate donors, have presented volumes as follows: F. A. Davis Company, 41; Lea & Febiger, 9; J. B. Lippincott Co., 43; W. B. Saunders Co., 91.

Other individual donors were as follows: Drs. F. H. Adler, C. E. Albrecht; Mr. R. Asnis; Drs. O. V. Batson, W. R. Bett, P. A. Bishop, T. Butterworth, B. Chance, G. W. Corner, D. L. Cowen, M. S. Fay, J. T. Freeman, P. S. Friedman, W. I. Gefter; Miss B. Gittings; Mrs. J. V. Klauder; Drs. W. Levy, S. H. Lewis, E. R. Long, R. W. Lorry, R. P. Mackay, G. Mann, S. Mudd; W. L. Necker, Mr. E. J. Neren; Drs. D. M. Pillsbury, H. Robertson, F. B. Rogers, H. G. Scheie, W. B. Shelley, M. H. Sloane, W. A. Steiger, P. E. Steiner, K. R. Sturgis, H. Swanberg, J. M. Thorington, and J. A. Wagner.

The *Transactions & Studies* was sent, either in exchange or as gift, to 536 organizations.

Theses and dissertations to the number of 435 have been received on exchange from the following European schools of medicine; Universities of Basel, Bern, Copenhagen, Geneva, Karolinska Institute of Stockholm, Leiden, Liège, Louvain, Uppsala, and Utrecht.

The Staff[9]

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Elliott H. Morse

Library Secretary
Mildred C. Gray

Processing Dept.

Muriel Zeldis, *Head*

Assistant Cataloger
Mrs. Kathryn E. Miragliotta

Cataloging Assistants
Mrs. Margaret Henry
Mrs. Theresa Perretta

Reference-Circulation Dept.

Mrs. Joyce S. Mingledorff, *Head*

Readers Service Assistants
Mrs. Julia O'Malley
Mrs. Kathryn Bernice Odom*
Mrs. Rosayne P. Tumilowicz*

Serials Dept.

Cecilia Chen Li, PH.D., *Head*

Serials Assistants
Mrs. Catherine Ledwell
Myrna Fisher*
Mrs. Doris Bridgman
Gayle Donahower*
Barbara Maurer*

Historical Collections

W. B. McDaniel, 2d, PH.D., *Curator*
Mrs. Lisabeth M. Holloway, *Associate Curator and Historical Cataloger*
Mrs. Betty Voigt,* *Typist*

Medical Documentation Service

Walter L. Bethel, PH.D., *Director*
Jean P. Carr, *Executive Secretary*
Mrs. Gail Groeneman* *Bibliographer*
Loretta Roddy* *Typist*
Patricia E. Roddy* *Typist*
Josephine L. Walsh, *Abstracter*

Paging Staff

Shirley Allen
Gloria Jean Culler
Terry Fox

[9] Library Staff list as of February 1, 1966.

* Part-time.

Paging Staff—Continued

Andrea L. Jancsura
Juncann M. Kasperowicz
Daniel Kelly
Steven J. Peitzman*
Josefa Sereda
Halina T. Wierzbicki*

Approved:
Samuel X Radbill, M.D.
Chairman, Library Committee

Annual Report of the Committee on the Mütter Museum and College Collections

The Mütter Museum of the College of Physicians has become more widely known because of publicity through published articles and photographs of the specimens in various magazines, and also from special exhibits. This has increased the attendance considerably in the past year, and people who previously only came to the library, finally found their way into the museum and realized that they had been neglecting an important part of the College.

The museum is open daily from 9 A.M. to 3:30 P.M., except on Saturdays and Sundays, and 2532 persons visited it this year. Besides the individuals from almost every state in the United States and many foreign countries, it plays host to large groups of medical students, from the medical colleges in the area, student nurses from various hospitals, high school students who contemplate professional careers, biology students from the public schools, and students of medical technology.

The colleges represented are Woman's Medical College, Temple University School of Medicine, Hahnemann Medical College, University of Pennsylvania School of Medicine, Drexel Institute of Technology, West Chester State College, Philadelphia College of Osteopathy, and Pennsylvania State College of Optometry.

Graduate or student nurses came from the Montgomery Hospital in Norristown, the Nazareth Hospital in Philadelphia, Chester County Hospital School of Nursing, Villanova University School of Nursing and St. Joseph's Hospital School of Nursing.

School groups also came from St. Leonard's Academy, Hussian School of Art, Franklin School of Science and Arts, and the Germantown Friends' School.

High Schools represented are Shoemaker, Edison, West Chester, Central, Clifton Heights, Roxborough, and South West High School from Hanover, Pennsylvania. Eighty students from New Rochelle High School came by bus from New York. They had come to Philadelphia to visit the Wistar Institute and, finding the specimens no longer there, were directed to the College where they arrived unannounced! When the Catholic Library Association met at the College, they also toured the museum.

So varied and numerous are the exhibits that even those who make frequent trips to the museum, find things that they had missed on a previous visit. This year, however, they will find two exhibits that are new. One is a collection of ancient bronze Roman surgical instruments that were taken from the Tiber River by workmen who were dredging in order to lay piling for a new bridge. They date back to the 2nd century A.D., are in excellent condition and were authenticated by Dr. Kenneth Matthews of the University Museum. Many probably served as domestic tools as well as surgical instruments.

We were indeed fortunate when the Wistar Institute thought of the Mütter Museum when they were disposing of some of their exhibits, and offered it four large handsome cases and their contents on a permanent loan. The cases were taken apart by Mr. Kolodziejski and his assistant, Mr. Bolton (no small undertaking), and transferred to the museum with the specimens, and here reassembled. The specimens were placed on the shelves and form a valuable and attractive exhibit. They

show dissections and models of the development of the human fetus, dissections showing the development of the vertebrate brain ranging from fish to man, teratological specimens of the human fetus, and head sections showing the anatomy of the interior of the skull. We recently received a request for a photograph of a specimen of Phocomelus in the collection, from Professor W. Lenz of the Münster University in Germany.

For some reason the interest in old medicine bags and cases seems to have been revived, and we have received many requests for photographs of some of those in the museum collection. Pictures of three of these appear in the September 1965 issue of M.D. Medical Newsmagazine, with an article entitled *Little Black Bag*.

Upon request, photographs of three of the old hypodermic syringes in the museum were sent to Lynette Trotter, of Aldus House in London, to be pictured in a book, *The History of Drugs*, that will be published in the United Kingdom, the United States and several European countries.

A photograph of the original Quartz-Piezo Electrometer, devised by Professor Pierre Curie and used by him and Mme. Curie in the earliest measurements of radium, was taken for Dr. Herbert S. Klickstein of the Albert Einstein Medical Center in Philadelphia.

Dr. Samuel X Radbill brought his class in pediatrics, as he does every year, to study instruments, old and modern, used in that field. Most of the students were from foreign countries and they were an especially interested group.

The 77th Thomas Dent Mütter Lecture was delivered by Robert C. Mellors, M.D., PH.D., on February 3, 1965. He is Professor of Pathology at Cornell University Medical College, Director of Laboratories and Associate Director of Research, Hospital for Special Research, New York. His subject was, *Immunological Mechanisms in Glomerulonephritis, Hypersensitivity and Autoimmunity.*

Mrs. Ella N. Wade was reappointed curator for the year 1965–1966.

College Collections

In connection with the Bicentennial of the Founding of the University of Pennsylvania School of Medicine, ten oil portraits of the College were loaned to the Philadelphia Museum of Art, together with a plaque showing the progress of fatigue in athletes, by Dr. R. Tait McKenzie. The Museum of Art had previously photographed twenty-five of the College portraits and has promised to furnish the College with copies of the prints.

In connection with this same anniversary, radio station WFIL took photographs of several items in the Mütter Museum which were added to the film which was televised on Channel 6 on October 30, 1965, at 4:30 P.M.

Historical objects from College Collections were loaned for the meeting in Chicago, in February, of the American College of Surgeons, and all were returned safely.

Other material was loaned to the University of Pennsylvania School of Medicine for exhibit during its bicentennial anniversary.

The Newman Galleries restored the portrait of S. Weir Mitchell by Dvorak, and the frames and portraits of Joseph Leidy, Joseph Parrish and William P. Dewees. New brass plates were purchased for several of the portraits, the former plates having become illegible.

For several years it has been the policy of the College to have most gifts catalogued in College Collections where they are available for loan, except those definitely presented to the Museum.

Dr. Fred B. Rogers presented a small French bronze bust of Hippocrates and a signed drawing of August von Wassermann. The drawing was added to the Sturgis Collection.

Dr. J. Monroe Thorington presented a number of votive offerings from Peru, Ecuador and Argentina. Some of these are of silver and others of native alabaster. They are dated late 18th and 19th centuries.

A Family Emergency Medicine Chest, dated 1860, was presented by *Mrs. Elizabeth H. Beahm*. This had belonged to her great-grandfather, Mr. Michael Maize, an Evangelical itinerate preacher, after whom the town of Maizeville, Pennsylvania, was named.

A small unique eight-day desk clock having two faces and formerly belonging to Dr. Arthur A. Stevens, was presented by *Dr. Truman G. Schnabel.*

Mrs. Ella N. Wade was reappointed custodian of College Collections for the year 1965–1966.

A. Reynolds Crane, M.D.
Chairman

List of College Lectures, 1965

6 January 1965

Moyer, Carl A. A Treatment of Burns (Nathan Lewis Hatfield Lecture II; *Transactions & Studies*, October 1965.)

3 February 1965

Mellors, Robert C. Immunologic Mechanisms in Glomerulonephritis: Hypersensitivity and Autoimmunity (Thomas Dent Mütter Lecture LXXVII; *Transactions & Studies*, July 1965.)

3 March 1965

Ellis, John R. Preventive Medicine in Medical Education: An Internist's Viewpoint (James M. Anders Lecture XLIV; *Transactions & Studies*, July 1965.)

7 April 1965

Durrer, Dirk. The Human Heart: Some Aspects of its Excitation (Mary Scott Newbold Lecture LXXXIX; *Transactions & Studies*, January 1966.)

19 May 1965

Joint Meeting of the Philadelphia County Medical Society and The College of Physicians of Philadelphia.

I. Presentation of the First Annual Kenneth E. Appel, M.D. Award to Robert E. Jones, M.D., Institute of the Pennsylvania Hospital.

II. Presentation of Certificates to Physicians who have completed fifty years in the practice of medicine. Certificates awarded by Richard A. Kern, M.D., Sc.D., LL.D., President, Pennsylvania Medical Society.

10 June 1965

At the Philadelphia County Medical Society: Presentation of the 42nd Annual Strittmatter Award to Thomas M. Durant, M.D., Sc.D., by W. Emory Burnett, M.D., Sc.D., Chairman, Strittmatter Award Committee. First meeting in the new Auditorium of the Philadelphia County Medical Society, 2100 Spring Garden Street. Address by Dr. Durant: Medical Education and Practice in Japan.

13 October 1965

Samter, Max. Drug Antigens and the Diseases Which They Produce (Hira S. Chouké Lecture VI; *Transactions & Studies*, January 1966.)

3 November 1965

Genest, Jacques. Renin-Angiotensin System and Human Hypertension (Mary Scott Newbold Lecture XC.)

19 November 1965

Champagne reception at the Philadelphia Museum of Art in conjunction with the exhibition, "The Art of Philadelphia Medicine", arranged to celebrate the Bicentennial of Medical Education in the United States, 1765–1965.

1 December 1965

Harlow, Harry F. The Primate Socialization Motives (Alvarenga Lecture XXV; *Transactions & Studies*, April 1966.)

Transactions of the Sections

SECTION ON MEDICAL HISTORY

8 February 1966

CLASSIC DESCRIPTIONS IN DIAGNOSTIC ROENTGENOLOGY: THE HISTORY OF DARK ADAPTATION. William J. Tuddenham, M.D.

THE EARLY DAYS OF OPHTHALMOLOGY AT THE UNIVERSITY OF PENNSYLVANIA. Daniel M. Albert, M.D., and Harold G. Scheie, M.D.

CONTEMPORARY HISTORY AND BIOGRAPHY IN PSYCHIATRY. DANIEL BLAIN, M.D. Kenneth E. Appel, M.D.

SECTION ON OPHTHALMOLOGY[1]

14 October 1965

OUR PHILADELPHIA OPHTHALMIC HERITAGE —DR. GEORGE MCCLELLAN AND DR. FITZWILLIAM SARGENT. Harold D. Barnshaw, M.D.

SURGICAL TREATMENT OF ESSENTIAL BLEPHAROSPASM. Michael I. Wolkowicz, M.D. (Discusser: Henry A. Shenkin, M.D.)

DIABETIC AND ARTERIOLARSCLEROTIC ALTERATIONS OF CHOROIDAL VISIBILITY. Thomas D. Duane, M.D., and Thomas Behrendt, M.D.*

11 November 1965

CRYOSURGERY. John M. McLean, M.D.*, Professor of Ophthalmology, Cornell University Medical College, New York City. (Twenty-eighth Annual de Schweinitz Lecture.)

[1] Abstracts of the presentations at this Section customarily appear in the *American Journal of Ophthalmology* and *A.M.A. Archives of Ophthalmology*.

* By invitation.

SECTION ON OTOLARYNGOLOGY[2]

3 February 1966

(Combined meeting, Section on Otolaryngology, The College of Physicians of Philadelphia, and the Philadelphia Laryngological Society.)

SURGERY OF THE ENDOLYMPHATIC SAC. George E. Shambaugh, Jr., M.D.* (The George M. Coates Memorial Lecture.)

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

5 October 1965

(Joint meeting at Lankenau Hospital with Pennsylvania Department of Health, Region Seven.)

THEME: HEALTH EDUCATION AND YOU. Keynote Speaker: William A. Steiger, M.D.

THE UNIVERSITY IN THE FOREFRONT OF COMMUNITY ACTION (*Transactions & Studies*, April 1966.)

7 December 1965

(Arthur Parker Hitchens Lecture X. Joint meeting with Pennsylvania Public Health Association, Region One.)

DELINQUENCY AND PARENTAL ROLES. Maurice E. Linden, M.D.*, Director of Mental Health, Philadelphia Department of Public Health.

[2] Abstracts of the presentations at this Section customarily appear in the *A.M.A. Archives of Otolaryngology*.

Officers, Committees, Sections and Administrative Staff of the College 1966

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Vice-President

Francis C. Wood

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William A. Steiger

Treasurer

Kendall A. Elsom

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Edward B. Krumbhaar†
J. Parsons Schaeffer
Thomas M. Durant

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To serve until January, 1967

Donald C. Geist
Joseph L. Finn

To serve until January, 1968

John Franklin Huber
Robert F. Norris

To serve until January, 1969

Thomas F. Nealon, Jr.
Paul O. Klingensmith

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The forenamed and the chairman of the Standing Committees*

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E. Howard Hinman
Edward H. McGehee
Lysle H. Peterson
Charles A. Uhle

Hall

Paul J. Grotzinger, ch'n
John B. Atkinson
Donald R. Cooper
John L. McClenahan
Brooke Roberts

Mütter Museum and College Collections

Nicholas Padis, ch'n
Clark E. Brown
Norman Learner

Publication

Fred B. Rogers, ch'n
Herman Beerman
Robert E. Jones

* The President is an *ex officio* member of all Standing Committees. † d. 16 March 1966.

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Elizabeth Kirk Rose
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Alfred M. Bongiovanni, ch'n
Rudolph C. Camishon
Donald R. Cooper
Claude R. Joyner, Jr.
Henry J. Tumen

Nathan Lewis Hatfield Prize and Lectureship

Hugh Montgomery, ch'n
Frank A. Elliott
Thomas F. Nealon, Jr.

Weir Mitchell Oration

Bernard J. Alpers, ch'n
Elliott L. Mancall
William L. Peltz
Charles Rupp
Henry A. Shenkin

The President and the Chairman of the Committee on Scientific Business, *ex officio*

Mary Scott Newbold Lectures

J. Russell Elkinton, ch'n
Gordon N. French
Kenneth E. Fry
The President and the Chairman of the Committee on Scientific Business, *ex officio*

Benjamin Musser Lectureship

W. Paul Havens, Jr., ch'n
J. Deaver Alexander
Alexander Rush

Hira S. Chouké Lectureship

Samuel E. Rynes, ch'n
George I. Blumstein
Burton Zweiman

Theodore F. Bach Memorial Lecture

George E. Farrar, Jr., ch'n
Philip R. Trommer
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Superintendent

THEODORE J. KOLODZIEJSKI

Fellows

February 5, 1966

ELECTED

1952. Abelson, Neva Martin, 32 Woodale Rd. (18)
1961. Adamson, William C., 1542 Susquehanna Rd., Rydal, Pa.
1926. Adler, Francis Heed, 313 S. 17th St. (3)
1959. Adlin, Albert, 1512 Lindley Ave. (41)
1949. Aegerter, Ernest E., 3400 N. Broad St. (40)
1953. Agerty, Horst A., 1111 N. 63rd St. (19151)
1960. Ainsworth, Thomas H., Jr., 960 County Line Rd., Bryn Mawr, Pa.
1964. Albert, Seymour M., 255 S. 17th St. (19103)
1963. Albright, Edwin P., 512 E. Mt. Airy Ave. (18)
1958. Alexander, John Deaver, Philadelphia General Hospital (4)
1962. Alexander, John Dewey, Jr., 330 S. 9th St. (7)
1935. Alpers, Bernard J., 111 North 49th St. (39)
1960. Ames, Mary D., 260 St. James Place (6)
1961. Amsterdam, Gerald H., Wyncote House, Wyncote, Pa.
1962. Annesley, William H., Jr., 39 Glendale Road, Upper Darby, Pa.
1961. Antiiony, Russell A., 385 Lancaster Ave., Haverford, Pa.
1961. Aponte, Gonzalo E., 1025 Walnut St. (7)
1930. Appel, Kenneth E., 111 N. 49th St. (39)
1905. Appelman, Leighton Francis, Limekiln Pike & Twining Rd., Glenside, Pa. (19038)
1960. Arey, James B., 2600 N. Lawrence St. (33)
1959. Arkless, Henry A., 255 S. 17th St. (3)
1922. Arnett, John H., 2116 Pine St. (3)
1952. Asii, Rachel, 255 S. 17th St. (3)
1952. Aston, Melville J., 6 Circle Drive, Margate, N.J. (08402)
1944. Atkins, Joseph P., 1201 Knox Rd., Wynnewood, Pa.
1956. Atkinson, John B., 410 Township Line Rd., Havertown, Pa. (19083)
1935. Atlee, John L., Jr., 37 E. Orange St., Lancaster, Pa.
1952. Atlee, William A., 37 E. Orange St., Lancaster, Pa.
1963. Austrian, Robert, Hospital of the University of Pennsylvania (4)
1958. Ayella, Alfred S., Jr., 1213 S. Broad St. (47)
1960. Bacon, Catherine L., 504 Howe Rd., Merion Station, Pa.
1937. Bacon, Emily P., 803 E. Darby Rd., Havertown, Pa. (19083)
1960. Bacon, Harry E., 255 S. 17th St. (3)
1958. Baer, Samuel, 5123 N. Broad St. (41)
1959. Baird, Henry Welles, III, 2600 N. Lawrence St. (33)
1952. Baier, Howard N., 3401 N. Broad St. (40)
1952. Baker, Howard W., 3401 N. Broad St. (40)
1963. Baker, Richard B., 1851 E. Allegheny Ave. (34)
1946. Baker, Walter W., 255 S. 17th St. (3)
1963. Balin, Howard, 330 S. 9th St. (7)
1957. Baltzell, William Hewson, 1530 Locust St. (2)
1940. Barba, Philip S., 120 Erdenheim Road (18)
1943. Barden, Robert P., 8835 Germantown Ave. (18)
1939. Barnshaw, Harold D., 526 Cooper St., Camden 2, N. J.

1957. Barr, S. Stanley, 255 S. 17th St. (3)
1939. Bartle, Harvey, Jr., Glenbrook Medical Bldg., 864 County Line Rd., Bryn Mawr, Pa.
1963. Bartuska, Doris G., Woman's Medical College (19129)
1963. Bassett, James G., 3300 Henry Ave. (19129)
1932. Batson, Oscar V., 3926 Pine St. (4)
1921. Bauer, Edward L., Alden Park Manor (44)
1933. Bauer, John T., 312 E. Second St., Moorestown, N. J.
1939. Baumann, Frieda, 200 N. Wynnewood Ave., Wynnewood, Pa.
1930. Beardwood, Joseph T., Jr., 1245 Highland Ave., Abington, Pa. (19001)
1952. Bedrossian, E. Howard, 4501 State Rd., Drexel Hill, Pa.
1935. Beerman, Herman, 255 S. 17th St. (3)
1942. Behrend, Albert, 1018 Melrose Ave. (26)
1945. Behrend, Bernard, 5910 Greene St. (44)
1934. Behrend, Moses, Rittenhouse Claridge, 18th & Walnut Sts. (3)
1949. Beizer, Lawrence H., 419 South 19th St. (46)
1936. Bell, Benjamin Tertius, 1941 Woodland Rd., Abington, Pa.
1956. Beller, Martin Leonard, 1936 Spruce St. (3)
1947. Bellet, Samuel, 2021 Spruce St. (3)
1956. Belmont, Owen, 5723 No. Park Ave. (41)
1959. Berk, Nathaniel G., 2534 W. Cheltenham Ave. (50)
1951. Bernstine, J. Bernard, 255 S. 17th St. (3)
1965. Berry, Richard G., 1025 Walnut St. (19107)
1956. Berry, Theodore J., 331 E. Lancaster Ave., Wynnewood, Pa.
1957. Biele, Albert M., 1530 Locust St. (2)
1964. Biele, Flora H., 1530 Locust St. (19102)
1918. Billings, Arthur E., 2020 Spruce St. (3)
1957. Birdsall, Thomas M., 255 S. 17th St. (3)
1949. Bishop, Edward H., 811 Spruce St. (7)
1933. Bishop, Paul A., 1347 Waverly Rd., Gladwyne, Pa.
1944. Blady, John V., Parkway House, 2201 Benjamin Franklin Pkwy. (30)
1960. Blake, Alton D., Jr., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1952. Blake, Paul O., 273 N. Lansdowne Ave., Lansdowne, Pa.
1958. Blakemore, William S., 419 S. 19th St. (46)
1917. Block, Frank B., A1124 Park Drive Manor (44)
1963. Block, Reuben, 1555 Haddon Ave., Camden, N. J.
1949. Blumstein, George I., 2039 Delancey St. (3)
1929. Bockus, Henry L., 250 S. 18th St. (3)
1962. Boggs, Thomas R., Jr., Children's Hospital, 1740 Bainbridge St. (46)
1928. Boles, Russell S., Rittenhouse Plaza, 1901 Walnut St. (3)
1923. Bond, Earl D., Bryn Mawr Court, Bryn Mawr, Pa.
1961. Bongiovanni, Alfred M., 1740 Bainbridge St. (46)
1948. Bookhammer, Robert S., 264 Forrest Rd., Merion, Pa.
1931. Bortz, Edward Le Roy, Lankenau Medical Bldg. (19151)
1936. Bostwick, Delazon Swift, 1523 Sweetbriar Rd., Gladwyne, Pa.
1947. Bourland, Henry S., 2219 Garret Rd., Drexel Hill, Pa.
1961. Bouzarth, William F., 3300 Henry Ave. (29)
1961. Bove, Frank A., 2301 Pennsylvania Ave. (30)
1954. Bowers, Paul A., 2031 Locust St. (3)
1942. Bowie, Morris A., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1963. Boyer, Randal A., Holy Redeemer Hospital, Meadowbrook, Pa.
1964. Brackin, John T., Jr., Abington Memorial Hospital, Abington, Pa.
1965. Brady, Anna M., 3302 W. Queen Lane (19129)

1959. Brady, Luther W., 230 N. Broad St. (19102)
1954. Bralow, S. Philip, 3701 N. Broad St. (40)
1942. Branen, William T., Whitby & Cypress Aves., Yeadon, Pa.
1921. Bransfield, John W., 2031 Locust St. (3)
1948. Braun, William, 406 Cooper St., Camden, N. J.
1953. Bray, Solomon S., 5575 N. Park Ave. (41)
1953. Breckenridge, Robert L., Our Lady of Lourdes Hosp., 1600 Haddon Ave., Camden 3, N. J.
1964. Brenman, Arnold K., 3701 N. Broad St. (19140)
1961. Breslow, Irwin H., 1924 Panama St. (19103)
1946. Briscoe, Clarence Conway, 811 Spruce St. (7)
1953. Brobeck, John R., Univ. of Pa. School of Medicine (4)
1958. Brody, Henry, Einstein Medical Center, York & Tabor Rds. (41)
1965. Brody, Jerome I., Graduate Hospital, 19th & Lombard Sts. (19146)
1952. Brody, Morris W., 1930 Chestnut St. (3)
1948. Brogan, Edmund J., 1020 Cedargrove Rd., Wynnewood, Pa.
1953. Brooke, John A., 1431 Spruce St. (2)
1958. Brooks, Frank P., Hospital of the Univ. of Pa. (4)
1936. Brown, Clark E., Lancaster Ave. & City Line Ave. (19151)
1932. Brown, Claude P., 1930 Chestnut St. (3)
1963. Browne, Laurence T., Presidential Apts., D126 (19131)
1961. Brunt, Manly Y., 111 N. 49th St. (39)
1939. Brust, Raymond M., 4710 Chester Ave. (43)
1953. Bucher, Robert M., 3401 N. Broad St. (40)
1961. Buerk, Minerva S., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1962. Burgoon, Carroll F., Jr., 804 Pine St. (7)
1940. Burnett, W. Emory, 3401 N. Broad St. (40)
1962. Burney, Leroy E., 3400 N. Broad St. (40)
1954. Burros, Harry M., 419 S. 19th St. (46)
1941. Butler, Miriam, Watersmeet, Glen Mills, Pa.
1957. Butterworth, Thomas, 411 Walnut St., Reading, Pa.
1965. Byron, Harold J., Wyncote House, Wyncote, Pa.
1966. Cahn, Milton M., 1930 Chestnut St. (19103)
1957. Calhoun, John Alfred, Jr., 214 Elm Ave., Swarthmore, Pa.
1958. Cameron, Charles S., 235 N. 15th St. (2)
1962. Camishion, Rudolph C., 1025 Walnut St. (7)
1952. Campbell, Edward W., Abington Memorial Hospital
1944. Campion, Richard J., Box 136, Springhouse, Ambler, Pa.
1964. Cancelmo, Jesse J., Jr., 337 W. Lancaster Ave., Wayne, Pa.
1931. Cantarow, Abraham, 1025 Walnut St. (7)
1935. Carey, Lawrence S., 2241 Garrett Road, Drexel Hill, Pa.
1931. Cariss, Walter L., 51 N. 39th St. (4)
1930. Carpenter, Chapin, 502 Chestnut Lane, Wayne, Pa.
1959. Carrington, Elsie R., Woman's Medical College (29)
1960. Carroll, Robert T., 1015 Sansom St. (7)
1917. Carson, John B., Newtown Square, Pa.
1956. Carty, James Byron, 51 Hampden Rd., Upper Darby, Pa.
1956. Casey, Paul R., 8350 Roosevelt Blvd. (15)
1943. Castigliano, S. Gordon, 853 Mt. Pleasant Rd., Bryn Mawr, Pa.
1949. Caswell, H. Taylor, 3401 N. Broad St. (40)
1954. Catenacci, Alfred J., 343 Winding Way, Merion Station, Pa.
1954. Cathcart, Richard T., Jefferson Hospital, 1025 Walnut St. (7)
1950. Chamberlain, Richard H., 3400 Spruce St. (4)

1939. Chamberlin, George W., Reading Hospital, Reading, Pa.
1966. Chamblin, William D., 3717 Chestnut St. (19104)
1945. Chance, Burton, Jr., 4400 Baltimore Ave. (19104)
1958. Channick, Bertram J., 3701 N. Broad St. (40)
1954. Charny, Charles W., 2039 Delancey Pl. (3)
1966. Chernoff, Benjamin, 6901 Old York Rd. (19126)
1960. Chirico, Anna-Marie, Hosp. of Univ. of Pa. (4)
1947. Chouké, Keiiar S., 4050 Forest Hill Ave., Apt. 3, Richmond, Va. (23225)
1945. Cianfrani, Theodore, 1930 Chestnut St. (3)
1939. Ciccone, Emmet F., 2021 Murray St. (15)
1960. Cinquino, Mario A., 1518 S. Broad St. (46)
1960. Clader, Stanley C., 825-A Glenbrook Ave., Bryn Mawr, Pa.
1951. Clagett, A. Henry, Jr., 515 W. Eighteenth St., Wilmington, Del. (19802)
1962. Clark, James E., 1015 Chestnut St. (7)
1951. Clark, John K., 36th & Spruce Sts. (4)
1947. Clark, Thomas Williams, 218 W. Chestnut Hill Ave. (18)
1963. Cleveland, Albert F., 615 Morgan Ave., Drexel Hill, Pa.
1958. Closson, Edward W., 2320 S. Broad St. (45)
1910. Cloud, J. Howard, Alden Park Manor (19144)
1949. Cohen, Louis B., 1320 Arrott St. (24)
1953. Cohen, Robert V., 520 Spring Ave., Elkins Park 17, Pa.
1965. Cohn, Edwin M., 1351 Tabor Rd. (19141)
1964. Cohn, Herbert E., 1025 Walnut St. (19107)
1934. Collins, Leon Howard, Jr., 133 S. 36th St. (4)
1943. Colonna, Paul C., 133 S. 36th St. (4)
1949. Conger, Kyril B., 3401 N. Broad St. (40)
1961. Coon, Julius M., 1025 Walnut St. (7)
1945. Coonel, Pauline, 47 E. Mt. Pleasant Ave. (19)
1930. Cooper, David A., 1328 Medford Rd., Wynnewood, Pa. (19096)
1953. Cooper, Donald R., Woman's Medical College, 3300 Henry Ave. (29)
1960. Cooper, Edward Sawyer, 6710 Lincoln Drive (19)
1947. Coppolino, John F., 1807 S. Broad St. (45)
1952. Corbit, John D., Jr., 3717 Chestnut St. (4)
1959. Cormeny, George F., 3818 Chestnut St. (4)
1965. Cornelison, Floyd S., Jr., 1025 Walnut St. (19107)
1941. Cornelius, Chalmers E., 119 Summit Ave., Jenkintown, Pa.
1911. Cornell, Walter S., Board of Public Education, Parkway and 21st St. (3)
1914. Corson, Edward F., 3047 Spring Mill Rd., Plymouth Meeting, Pa.
1959. *Cowan, Capt. John S., MC, USN, Commanding Officer, U. S. Naval Hospital (19145)
1940. Cowan, Thomas H., 1930 Chestnut St. (3)
1966. Cram, Robert H., 918 County Line Rd., Bryn Mawr, Pa. (19010)
1947. Crane, A. Reynolds, Pennsylvania Hospital (7)
1937. Crane, Martin P., 4701 Pine St. (43)
1952. Crellin, J. Antrim, 1930 Chestnut St. (3)
1955. Crist, Walter A., 211 N. 5th St., Camden, N. J.
1963. Crosley, Archer P., Jr., The Presbyterian Hospital (4)
1921. Crossan, Edward T., Buttonwood Hall, Conshohocken, Pa.
1959. Cullen, Milton L., 1936 Cottman Ave. (19111)
1962. Cunningham, John D., 3400 Spruce St. (4)
1934. Custer, R. Philip, 643 Moreno Road, Narberth, Pa.

* Military Service.

1958. D'Alonzo, Walter A., 1647 S. 15th St. (45)
1938. Dannenberg, Arthur M., Sr., 235 S. 15th St. (2)
1951. Daugherty, Earl A., 2818 W. Girard Ave. (30)
1953. Davie, John H., 37 S. 20th St. (3)
1947. Davis, C. Nelson, 524 Howe Rd., Merion Station, Pa.
1936. Davis, David M., 960 County Line Rd., Bryn Mawr, Pa. (19010)
1957. Davis, John Evan, Tedwyn Apts., 840 Montgomery Ave., Bryn Mawr, Pa.
1951. Davis, J. Wallace, 135 S. 18th St. (3)
1961. Dawber, Bryan A., Penn Mutual Life Insurance Co. (5)
1963. Day, H. James, Temple University Hospital (19140)
1935. Deaver, J. Montgomery, Lankenau Medical Bldg. (19151)
1957. Decker, John Paul, Pennsylvania Hospital (7)
1957. Dees-Porch, Frances, Glendale Road & Chestnut Sts., Upper Darby, Pa.
1947. Dehne, Theodore L., Adams Avenue and Roosevelt Blvd. (24)
1935. Deibert, Irvin Elmer, Pen Key Club, Islamorada, Fla.
1958. Deitz, George W., III, 2240 Pine Rd., Huntingdon Valley, Pa.
1965. Delaney, William E., III, 11th & Sansom Sts. (19107)
1955. De Long, Samuel L., 223 Lancaster Ave., Devon, Pa.
1952. DeLuca, Charles Q., 255 S. 17th St. (3)
1952. De Orsay, Ralph H., 1241 Lindale Ave., Drexel Hill, Pa.
1951. De Palma, Anthony F., 248 S. 21st St. (3)
1963. Derham, Robert J., McClatchy Bldg., Upper Darby, Pa.
1966. deRivas, Carmela F., Stanbridge & Sterigere Sts., Norristown, Pa.
1959. DeTuerk, John J., 1930 Chestnut St. (3)
1959. Dickens, Helen O., P. O. Box 9336 (39)
1958. Dickstein, Benjamin, 6810 Castor (24)
1956. Dietrich, Herbert James, Jr., Hospital of the University of Pennsylvania (4)
1952. Digilio, Victor A., 2200 St. James Place (17)
1963. DiMarino, Anthony J., 735 Delaware St., Paulsboro, N. J.
1960. Dinon, Louis R., 330 S. 9th St. (7)
1920. Doane, Joseph C., 5286 34th Ave., N., St. Petersburg, Fla. (33710)
1948. Dohan, Francis Curtis, 80 Princeton Road, Cynwyd, Pa.
1954. Donaldson, James B., 1901 Walnut St. (3)
1946. Donnelly, Andrew J., 33rd and Powelton Ave. (4)
1937. Donnelly, Robert T. M., 5205 N. Broad St. (41)
1962. Dorman, Philip J., Fidelity Mutual Life Insurance Co. (1)
1964. Dratman, Mary B., Woman's Medical College, Henry Ave. & Abbottsford Road (19129)
1952. Drayer, Calvin S., 111 N. 49th St. (39)
1949. Dripps, Robert D., 3400 Spruce St. (4)
1944. Dublin, George J., 1930 Chestnut St. (3)
1935. Duncan, Garfield G., 330 S. 9th St. (7)
1953. Dupler, Donald A., 4028 Walnut St. (4)
1942. Durant, Thomas M., 3401 N. Broad St. (40)
1942. Dyer, W. Wallace, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1962. D'Zmura, Thomas L., Presidential Apts., City Line Ave. & Presidential Blvd. (19131)
1936. Easby, Mary Hoskins, R. D. 1, Burlington, Vt.
1948. Eaton, Francis H., 4007 Chestnut St. (39)
1964. Eberlein, Walter R., 1740 Bainbridge St. (19146)
1937. Edeiken, Joseph, 2130 Delancey Pl. (3)
1944. Eger, Sherman A., 255 S. 17th St. (3)

1944. Ehrich, William E., 540 W. Hortter St. (19)
1956. Eiman, John W., Abington Memorial Hospital, Abington, Pa.
1962. Eisenberg, Samuel W., 3536 N. Broad St. (40)
1959. Eisenhower, James S. D., Jr., 2704 Pacific Ave., Wildwood, N. J.
1958. Eisman, Sylvan H., 3600 Spruce St. (4)
1959. Elias, Elmer J., 10 Monticello Ave., Trenton, N. J.
1949. Elkinton, J. Russell, Oak Lane, Moylan, Pa.
1961. Elliott, Frank A., 807 Spruce St. (7)
1957. Ellis, Richard A., 255 S. 17th St. (3)
1955. Ellis, Samuel, 541 S. 46th St. (43)
1939. Ellis, Van Mashburn, 1528 Spruce St. (2)
1928. Ellison, Richard T., Medical Office Bldg., 1245 Highland Ave., Abington, Pa. (19001)
1936. Ellson, J. Vernon, Glendale Road & Chestnut St., Upper Darby, Pa.
1937. Elsom, Kendall A., Scott Paper Co. (13)
1932. Engel, Gilson C., Lankenau Medical Bldg. (19151)
1945. English, O. Spurgeon, 449 Righters Mill Rd., Narberth, Pa.
1965. Epstein, Isadore S., 5219 Lebanon Ave. (19131)
1942. Erb, William H., 133 S. 36th St. (4)
1957. Erdman, William James, II, 3400 Spruce St. (4)
1965. Erslev, Allan J., 1015 Sansom St. (19107)
1950. Ersner, Matthew S., 1915 Spruce St. (3)
1957. Etzl, Michael M., 9025 Frankford Ave. (14)
1954. Evans, William W., Box 2, Bryn Mawr, Pa.
1955. Eynon, Harold K., Route 70 at East Gate, Barclay Farm, Haddonfield, N. J.
1946. Farell, David M., 1912 Spruce St. (3)
1903. Farr, Clifford B., Railroad Ave. & County Line Rd., Bryn Mawr, Pa.
1945. Farrar, George Elbert, Jr., 528 Scott Rd., Gladwyne, Pa.
1953. Farrell, Harry L., 1930 Chestnut St. (3)
1964. Faust, Herbert A., 245 N. Broad St. (19107)
1935. Ferguson, Lewis Kraeer, 419 S. 19th St. (46)
1936. Fetter, Ferdinand, 322 S. 21st St. (3)
1945. Fetter, John S., 842 Worrell Rd., Jenkintown, Pa.
1935. Fetter, Theodore R., 255 S. 17th St. (3)
1952. Fields, Harry, 133 S. 36th St. (4)
1959. Fineberg, Charles, 255 S. 17th St. (3)
1955. Finestone, Albert J., 3701 North Broad St. (40)
1960. Finkbiner, Rodman B., 811 Spruce St. (7)
1943. Finkelstein, Arthur K., Graduate Hospital (46)
1955. Finkelstein, David, 419 S. 19th St. (46)
1955. Finley, John K., 527 Welsh St., Chester, Pa.
1954. Finn, Joseph L., 8014 Burholme Ave. (11)
1947. First, Arthur, 1714 Spruce St. (3)
1954. Fischer, Carl C., Girard College (21)
1950. Fischer, H. Keith, School Lane House, 5450 Wissahickon Ave. (19144)
1962. Fisher, George R., III, 801 Spruce St. (7)
1958. Fisher, Robert M., 118 Airdale Rd., Rosemont, Pa.
1956. Fite, Franklin K., Germantown Hospital (44)
1952. Fitts, William T., Jr., 3400 Spruce St. (4)
1952. Flexner, Louis B., 248 Anatomy-Chemistry Bldg., Univ. of Pa. (4)
1928. Flick, John B., 819 Black Rock Rd., Gladwyne, Pa.
1939. Flippin, Harrison F., Lankenau Hospital (51)

1957. Fornwalt, George R., 47 Copley Rd., Upper Darby, Pa.
1954. Forster, H. Walter, Jr., 37 S. 20th St. (3)
1960. Foulger, John H., 601 Rockwood Rd., Wilmington, Del. (2)
1941. Fox, C. Calvin, 1806 Spruce St. (3)
1963. Fox, Eva F., Woman's Medical College (19129)
1963. Frank, Paul E., York Road & Summit Ave., Hatboro, Pa.
1963. Frank, Robert L., 514 Cooper St., Camden 2, N. J.
1959. Frankel, Kalman, 1424 Pepper Rd., Rydal, Pa.
1955. Frayer, William C., 37 S. 20th St. (3)
1941. Frazier, William Doane, 419 Gilpin Rd., Narberth Pa.
1952. Freed, Herbert, 255 S. 17th St. (3)
1956. Freeman, Joseph T., 8-A Rittenhouse Plaza (3)
1963. Freiman, Henry D., 1500 Hellerman St. (49)
1958. Freiwald, Milton J., 222 S. 19th St. (3)
1964. French, Gordon N., Misericordia Hospital (19143)
1955. Friedenberg, Zachary B., 133 S. 36th St. (4)
1951. Friedman, Paul Sigmund, 1422 Chestnut St. (2)
1960. Friedman, Sidney, 1740 Bainbridge St. (46)
1958. Frisch, Frederick, 888 Glenbrook Ave., Bryn Mawr, Pa.
1937. Fritz, Herbert H., Pennswood Rd., Bryn Mawr, Pa.
1961. Frobese, Alfred S., Abington Memorial Hosp., Abington, Pa.
1953. Fruchter, Joseph M., The Philadelphian, 2401 Pennsylvania Ave. (19130)
1940. Fry, Kenneth E., 1719 Rittenhouse Sq. (3)
1935. Fry, Wilfred Eyles, 1930 Chestnut St. (3)
1963. Furgiuele, Francis P., 5430 Greene St. (19144)
1937. Furlong, Thomas F., Jr., Times Medical Building, Ardmore, Pa.
1964. Galligan, William J., 2909 Garrett Road, Drexel Hill, Pa.
1954. Gambescia, Joseph M., 1422 Race St. (2)
1951. Garlichs, Richard W., 216 N. Manoa Road, Havertown, Pa.
1931. Garner, Vaughn C., 447 East Wadsworth St. (19)
1953. Garnet, James D., 807 Spruce St. (7)
1959. Gartland, John J., 269 S. 19th St. (3)
1950. Garvin, Eugene J., 533 S. 46th St. (43)
1952. Gefter, William I., 1900 Rittenhouse Square (3)
1935. Geist, Donald C., 301 E. City Line, Bala-Cynwyd, Pa.
1955. Gelfand, David, 1722 Pine St. (3)
1965. Georges, Thomas W., Jr., 3401 N. Broad St. (19140)
1941. Gershon-Cohen, J., 255 S. 17th St. (3)
1959. Gerson, Irvin M., Cedarbrook Apts., Cedarbrook Hills, Wyncote, Pa. (19095)
1955. Gettes, Bernard C., 128 Overhill Rd., Cynwyd, Pa.
1963. Giambalvo, Giacchino P., 818 N. 63rd St. (19151)
1965. Gianakon, Harry G., 111 N. 49th St. (19139)
1934. Gibbon, John H., Jr., 1025 Walnut St. (7)
1939. Gibson, Glen Gregory, 2031 Locust St. (3)
1944. Gifford, Edward S., Jr., 1913 Spruce St. (3)
1956. Gilbert, Philip D., Cooper Hospital, Camden, N. J.
1947. Giletto, Basil J., 2020 Locust St. (3)
1955. Gill, Robert J., 801 Spruce St. (7)
1922. Gilmour, William R., 6616 Woodland Ave. (42)
1952. Gilpin, Sherman F., Jr., 1023 Beury Building, 3701 N. Broad St. (40)
1963. Gindhart, Floyd D., 1213 Hamilton Avenue, Trenton, N. J.
1965. Ginley, Thomas H., Jr., The Iroquois, 47th St. & City Line Ave. (19151)

1949. Ginsburg, Isadore W., 3401 N. Broad St. (40)
1958. Girsh, Leonard S., 3701 N. Broad St. (40)
1954. Gislason, Gerhard J., 245 N. Broad St. (7)
1964. Gloeckner, M. Louise C., 110 E. Fourth Ave., Conshohocken, Pa.
1962. Gold, David A., 5587 N. Park Ave. (41)
1956. Goldberg, Harry, 7913 Rolling Green Rd., Cheltenham, Pa.
1965. Goldburgh, Warren P., 1932 Spruce St. (19103)
1958. Golub, Leib J., 136 S. 16th St. (2)
1963. Goluboff, Bernard, 413 W. Mermaid Lane (19118)
1965. Goodman, David H., 6816 Castor Ave. (19149)
1956. Goracci, Armando F., 2040 Poplar St. (30)
1937. Gordon, William, 5345 Spruce St. (39)
1964. Gottlieb, Harry, 5603 Greene St. (19144)
1964. Gottlieb, Philip M., 818 Medical Arts Bldg., 16th & Walnut Sts. (19102)
1965. Gould, R. John, Delaware County Memorial Hospital, Drexel Hill, Pa.
1956. Gouley, Benjamin, 5577 N. Park Ave. (41)
1966. Gowen, George F., Misericordia Hospital (19143)
1957. Grahn, Henry Victor, 5132 Chester Ave. (43)
1926. Grant, Francis Clark, 750 Germantown Pike, Lafayette Hill, Pa.
1965. Grassi, Michael O. A., 2038 Locust St. (19103)
1965. Greenbaum, Charles H., 6810 Castor Ave. (19149)
1940. Greene, Lloyd B., 803 Spruce St. (7)
1952. Greening, Roy R., Dept. of Radiology, Jefferson Hospital (7)
1958. Greenspan, Benjamin, 1319 W. Tabor Rd. (41)
1955. Greenstein, Raphael H., 1710 Pine St. (3)
1941. Groff, Robert A., Univ. of Pa. Hospital (4)
1952. Grotzinger, Paul J., 2121 Valley Rd., Huntingdon Valley, Pa.
1952. Grove, D. Dwight, 230 N. Broad St. (2)
1966. Guthrie, Marshall B., 1500 Spring Garden St. (19101)
1945. György, Paul, Univ. of Pa. School of Medicine (4)
1935. Hadden, Samuel B., 250 S. 18th St. (3)
1945. Hahn, George A., 255 S. 17th St. (3)
1964. Hall, John H., 3401 N. Broad St. (19140)
1955. Hallahan, John D., 104 W. Front St., Media, Pa.
1951. Hallett, Joseph W., 136 S. 16th St. (2)
1961. Hammett, Van Buren O., 249 N. Broad St. (19107)
1959. Hampton, Louis J., 300 Highland Ave., Hanover, Pa. (17331)
1954. Hand, B. Marvin, 1801 Pennsylvania Blvd. (3)
1938. Hand, John G., 1724 Pine St. (3)
1964. Hanes, Robert B., 501 Long Lane, Upper Darby, Pa.
1947. Hanes, William James, 218 E. Beechtree Lane, Wayne, Pa.
1963. Hanhausen, Edward H., 418 E. Lancaster Ave., Wayne, Pa.
1950. Hansen, A. Victor, 910 Centennial Rd., Penn Valley, Narberth, Pa. (19072)
1957. Harasym, Emil L., 5416 North 5th St. (20)
1956. Harbert, Frederick, Jefferson Hospital (7)
1952. Harer, W. Benson, State Rd. & Rogers Ave., Bywood, Pa.
1951. Harkins, Herbert P., 1930 Chestnut St. (3)
1963. Harris, Charles, 5301 Old York Road (41)
1962. Harris, James R., 3222 W. Penn St. (19129)
1959. Harris, James S. C., 5401 Wayne Ave. (44)
1965. Harris, John H., Jr., Carlisle Hospital, Carlisle, Pa.
1948. Harris, T. N., 5112 Woodbine Ave. (31)

1929. Harrison, Francis G., 1900 Spruce St. (3)
1964. Hart, Alonzo W., 847 N. 63rd St. (19151)
1926. Hartmann, Fred L., 1914 Pine St. (3)
1946. Harvey, Edith E., 406 York Rd., Jenkintown, Pa.
1947. Harvey, Rolfe Marsh, 669 Mill Rd., Villanova, Pa.
1961. Harvie, Fred H., 3400 Spruce St. (4)
1935. Haskell, Benjamin F., 1427 Spruce St. (2)
1958. Haupt, George J., Lankenau Medical Bldg. (51)
1960. Hausman, David H., Pennsylvania Hospital, 8th & Spruce Sts. (7)
1947. Havens, Walter Paul, Jr., 139 Cheswold Lane, Haverford, Pa.
1963. Hayes, Merrill B., 710 Madison St., Chester, Pa.
1952. Hayllar, Benjamin L., 803 Spruce St. (7)
1961. Hayward, Malcolm L., 111 N. 49th St. (39)
1961. Heath, Frederick K., Merck Sharp and Dohme, West Point, Pa.
1964. Heath, Robert D., Lankenau Medical Bldg. (19151)
1957. Hedges, Thomas R., Jr., 330 South 9th St. (7)
1961. Heggestad, Gilman E., Conestoga Medical Bldg., Bryn Mawr, Pa.
1965. Heil, Charles G., Jr., The Benson East, Jenkintown, Pa. (19046)
1965. Heine, William L., 5579 N. Park Ave. (19141)
1944. Herbut, Peter A., Dept. of Pathology, Jefferson Medical College Hospital (7)
1954. Herron, James R., 1486 Haddon Ave., Camden 3, N. J.
1963. Hesch, Joseph A., Misericordia Hospital (19143)
1949. Heyl, W. Meredith, 100 W. Coulter St. (44)
1956. Hildreth, Eugene A., Hospital of the University of Pennsylvania (4)
1961. Hilferty, Daniel J., Jr., Sutton Terrace Apts., 50 Belmont Ave., Bala-Cynwyd, Pa.
1952. Hinkson, DeHaven, 329 N. 40th St. (4)
1962. Hinman, E. Harold, 1025 Walnut St. (7)
1924. Hirst, John C., 2d., 1821 Spruce St. (3)
1943. Hitschler, William J., Bethlehem Pike & Summit (18)
1944. Hneleski, Ignatius S., 802 S. 48th St. (43)
1943. Hockaday, Agnes, 316 Shadeland Ave., Drexel Hill, Pa.
1939. Hodes, Philip J., Dept. of Radiology, Jefferson Medical College (7)
1947. Hodges, John H., 1025 Walnut St. (7)
1963. Hoffman, Carl J., 2901 Cottman Ave. (19149)
1959. Hoffman, Francis H., 3401 N. Broad St. (40)
1948. Hoffman, George L., Jr., 133 S. 36th St. (4)
1965. Holfelner, Edward D., Chestnut St. & Ashby Road, Upper Darby, Pa.
1954. Hollander, George, 3500 Vista St. (36)
1949. Hollander, Joseph L., 36th & Spruce Sts. (4)
1964. Holling, Herbert E., 3400 Spruce St. (19104)
1951. Hollis, Charles B., 28 W. School Lane (44)
1952. Holloway, Edward E., 1736 Pine St. (3)
1966. Holly, Roy G., 1025 Walnut St. (19107)
1966. Holter, F. Robert, 1911 Spruce St. (19103)
1949. Hopkins, Henry U., Garden Court Plaza, 47th & Pine Sts. (43)
1953. Horan, Charles A., 734 N. 63rd St. (19151)
1946. Horan, Gerald W., Marple-Newtown Medical Bldg., Newtown Square, Pa.
1947. Horwitz, Orville, Hospital of the University of Pennsylvania (4)
1950. Houlihan, Carl T., 207 McClatchy Bldg., Upper Darby, Pa.
1944. Housel, Edmund L., 255 S. 17th St. (3)
1928. Houser, Karl Musser, 170 Lakeside Rd., Ardmore, Pa. (19003)

1958. Howard, John M., 230 N. Broad St. (2)
1964. Howell, Doris A., 3300 Henry Ave. (19129)
1948. Howland, Alvin Wilcox, School Lane House (44)
1946. Howson, John Yeatts, 316 Lancaster Ave., Wayne, Pa.
1951. Hubbard, John P., 133 S. 36th St. (19104)
1947. Huber, John Franklin, Temple University School of Medicine (40)
1937. Hughes, Joseph, 111 N. 49th St. (39)
1939. Hughes, P. Boland, 419 Hillbrook Rd., Bryn Mawr, Pa.
1951. Hundley, J. Warren, 3818 Chestnut St. (4)
1954. Hunsicker, William C., Jr., 255 S. 17th St. (3)
1946. Hunt, William T., Jr., 6 Penn Center Plaza (3)
1921. Hunter, Robert John, 928 N. 63rd St. (19151)
1952. Hyman, Harold L., 3401 N. Broad St. (40)
1950. Imbriglia, Joseph E., 329 Shadeland Ave., Drexel Hill, Pa.
1949. Ingraham, Norman R., Jr., Stenton and Whitemarsh Aves. (18)
1957. Isaacson, Howard, Haverford Ave. & Drexel Rd. (19151)
1951. Isard, Harold J., Albert Einstein Medical Center, 5th & Reed Sts. (47)
1951. Israel, Harold L., 302 S. 19th St. (19103)
1947. Israel, S. Leon, 807 Spruce St. (7)
1947. Jaeger, Rudolph, Jefferson Bldg., 1015 Chestnut St. (7)
1966. Jannett, Andrew F., Packard St., Hammonton, N. J.
1965. Jenkins, B. Wheeler, 1526 E. Upsal St. (19150)
1943. Johnson, Julian, 3400 Spruce St. (4)
1959. Johnson, Robert G., 1015 Walnut St. (7)
1938. Johnson, Thomas A., 135 S. 18th St. (3)
1952. Jonas, Karl C., 2601 Parkway (30)
1963. Jones, Robert E., 111 N. 49th (39)
1963. Joseph, Rosaline R., 3401 N. Broad St. (40)
1961. Joyner, Claude R., Jr., 3400 Spruce St. (4)
1957. Kacher, Leon, 2037 Pine St. (3)
1957. Kane, Sydney H., 3458 Cottman Ave. (49)
1948. Kaplan, Louis, 2040 Pine St. (3)
1964. Kaplan, S. Richard, 419 S. 19th St. (19146)
1938. Kasper, Kelvin A., 135 S. 18th St. (3)
1966. Kassay, Dezso, 1 Summit St. (19118)
1958. Kasser, Max D., 37 S. 20th St. (3)
1945. Katz, G. Henry, 111 N. 49th St. (39)
1941. Kauffman, M. Luther, Medical Arts Bldg., Jenkintown, Pa.
1947. Kay, Calvin Frederick, Univ. of Pa. Hospital (4)
1954. Kaye, Robert, Children's Hospital, 1740 Bainbridge St. (46)
1947. Keefer, George Pfahler, 136 S. 16th St. (2)
1963. Keeley, Francis X., Professional Bldg., 1533 Haddon Ave., Camden, N. J.
1966. Keeney, Arthur H., Wills Eye Hospital (19130)
1949. Keiserman, Joseph, 1900 John F. Kennedy Blvd. (19103)
1959. Keitel, Hans G., 1025 Walnut St. (7)
1965. Kellow, William F. T., 235 N. 15th St. (19102)
1932. Kelly, Herbert T., 1830 Delancey Place (19103)
1961. Kelly, William E., 111 N. 49th St. (39)
1965. Kennedy, Charles, 1740 Bainbridge St. (19146)
1941. Kennedy, Patrick J., 32 Hampden Rd., Upper Darby, Pa.
1948. Kern, Franklin Moore, 903 Nicholson Rd., Wynnewood, Pa.
1921. Kern, Richard A., Temple University Hospital, 3401 N. Broad St. (40)

1935. Keyes, Baldwin L., 2031 Locust St. (3)
1936. King, Orville C., 330 S. 9th St. (7)
1952. Kirshner, Jacob J., 1930 Chestnut St. (3)
1960. Kitchell, J. Roderick, Abington Hospital Medical Office Bldg., 1245 Highland Ave., Abington, Pa. (19001)
1920. Klein, Thomas, 250 S. 18th St. (3)
1952. Kleinbart, Morris, 1922 Pine St. (3)
1954. Kligman, Albert M., 36th & Spruce Sts. (4)
1934. Kline, Oram R., 514 Cooper St., Camden, N. J.
1959. Kline, Oram R., Jr., 406 Cooper St., Camden 2, N. J.
1948. Klingensmith, Paul O., Med. Science Bldg., Lankenau Hosp. (19151)
1958. Klingensmith, Walter C., 3600 Spruce St. (4)
1956. Klinghoffer, June F., Woman's Medical College (29)
1932. Klopp, John W., Gwynedd Valley, Pa.
1960. Knopf, Carl L., 5312 Spruce St. (39)
1960. Knorr, John K., 3rd, Lankenau Medical Bldg. (19151)
1959. Knowles, Harry J., 255 S. 17th St. (3)
1945. Kobler, H. B., School Lane House, 5450 Wissahickon Ave. (19144)
1959. Koiwai, Eichi Karl, 235 N. 15th St. (2)
1963. Kolbe, Henry W., Philadelphia General Hospital (19104)
1957. Koltes, John A., 530 Spring Lane (19128)
1936. Konzelmann, Frank Williamson, Shore Memorial Hosp., Somers' Point, N. J.
1949. Koop, C. Everett, 1740 Bainbridge St. (46)
1964. Koppel, Max M., 7310 Castor Ave. (19115)
1952. Kornblueh, Ignio H., Welsh Rd. & Verree Rd. (15)
1958. Kovach, Coleman W., 2031 Locust St. (3)
1941. Krall, J. Thomas, 85 N. Lansdowne Ave., Lansdowne, Pa.
1948. Kramer, David W., 2007 Pine St. (3)
1954. Krasnoff, Sidney O., Tabor Medical Bldg., York & Tabor Roads (41)
1944. Krauss, Frederick Harold, 136 S. 16th St. (2)
1952. Kravitz, Charles H., 626 Ashbourne Rd., Elkins Park, Pa.
1964. Kremens, Victor, 60 E. Township Line Road, Elkins Park, Pa.
1949. Kressler, Robert J., 330 S. 9th St. (7)
1941. Krewson, William E., 3rd, 1930 Chestnut St. (3)
1914. Krumbhaar, Edward B., P. O. Box 4056 (18)
1947. Kuhlenbeck, Hartwig, Woman's Medical College, 3300 Henry Ave. (29)
1964. Kustrup, John F., 1418 S. Broad St., Trenton, N. J.
1947. La Boccetta, Alfred Charles, Philadelphia General Hospital, 34th St. & Curie Ave. (4)
1952. Lachman, John W., 3401 N. Broad St. (40)
1963. LaFia, David J., Methodist Hospital Medical Bldg. (19148)
1951. Lame, Edwin L., 51 N. 39th St. (4)
1950. Lamont, Austin, 3400 Spruce St. (4)
1946. Lampe, William T., 4207 Tyson Ave. (35)
1962. Landis, Harry P., Jr., 901 Columbia Ave., Palmyra, N. J.
1963. Lang, Leonard P., 1009 Park Place, Wilmington, Del.
1952. Lang, Warren R., 1012 Walnut St. (7)
1941. Langner, Paul H., Jr., 1208 Edmonds Ave., Drexel Hill, Pa.
1945. Lansbury, John, 3401 N. Broad St. (40)
1926. Laws, George M., 1907 Spruce St. (3)
1950. Learner, Norman, 3701 N. Broad St. (40)
1920. Leavitt, Frederic Headley, 1527 Pine St. (2)

1941. Leberman, Paul R., Hospital of the University of Pennsylvania (4)
1957. Lee, Charles Trumbull, Jr., 33 E. Chestnut Hill Ave. (18)
1952. Lehman, J. Stauffer, 230 N. Broad St. (2)
1961. Leibfried, Jane M., 5501 Greene St. (44)
1951. Leivy, Frank E., 135 S. 19th St. (19103)
1944. Lell, William A., 333 S. 18th St. (3)
1935. Lemmon, William T., 133 S. 36th St. (4)
1965. Leopold, Howard C., 4623 York Rd. (19140)
1955. Leopold, Robert L., 269 S. 19th St. (3)
1944. Lettiere, Anthony J., 425 E. State St., Trenton, N. J.
1965. Levenson, Carl, Albert Einstein Medical Center, N. D. (19141)
1933. Levering, J. Walter, 1322 Rydal Rd., Rydal, Pa. (19046)
1959. Levick, Leonard J., 1300 E. Cliveden St. (19)
1958. Levine, Samuel, 7100 N. 19th St. (26)
1964. Levit, Edithe J., 133 S. 36th St. (19104)
1964. Levit, Samuel M., 1910 Spruce St. (19103)
1958. LeWinn, Edward B., Wyncote, Pa.
1915. Lewis, Fielding O., Providence Road, Media, Pa.
1960. Lewis, George C., Jr., 230 N. Broad St. (2)
1964. Leymaster, Glen R., Woman's Medical College, 3300 Henry Ave. (19129)
1955. Lieberman, George E., 269 S. 19th St. (19103)
1956. Likoff, William, 249 N. Broad St. (2)
1962. Lilley, George W., 316 W. 9th St., Chester, Pa.
1940. Limberger, William A., 301 S. Church St., West Chester, Pa.
1958. Lin, David Y. P., 2222 S. Broad St. (45)
1938. Lindauer, M. August, 133 S. 36th St. (4)
1956. Lindquist, John N., 422 Sabine Ave., Wynnewood, Pa.
1927. Lindsey, Walter H., 102 Park Drive, Highland Park, Doylestown, Pa.
1936. Lintgen, Charles, 1930 Chestnut St. (3)
1958. Lipschutz, Arthur, 7974 Fayette St. (19)
1959. Lipshutz, Herbert, 807 Spruce St. (19107)
1953. Lipsius, Edward L., 319 S. 16th St. (3)
1959. Little, Ralph B., 111 N. 49th St. (39)
1944. Livezey, Mary M., 8835 Germantown Ave. (19118)
1936. Llewellyn, Thomas H., 910 N. 63rd St. (19151)
1907. Lodholz, Edward, The Fairfax, 43rd & Locust Sts. (4)
1963. London, Russell I., 6800 Castor Ave. (49)
1951. Long, Joseph P., 1930 Chestnut St. (3)
1935. Long, William L., 2038 Locust St. (3)
1931. Longaker, Edwin P., 41 E. Montgomery Ave., Ardmore, Pa.
1951. Lorber, Stanley H., 3701 N. Broad St. (40)
1961. Lorry, Ralph W., 1247 E. Luzerne St. (24)
1960. Lovett, B. Frank, 300 Broadway, Camden, N. J.
1963. Lubowitz, Richard M., Benson East Apts., Jenkintown, Pa.
1936. Lucchesi, Pascal Francis, 601 E. Gorgas Lane (19)
1960. Lucine, Albert A., 345 S. 19th St. (3)
1932. Lukens, Francis D. W., Univ. of Pa. Hospital (4)
1939. Luongo, Romeo A., 2054 Locust St. (3)
1947. Lurie, Max B., 5515 Wissahickon Ave. (19144)
1951. Luscombe, Herbert A., 136 S. 16th St. (2)
1952. Lutman, Frank C., 100 W. Coulter St. (44)
1919. Lynch, Frank B., Jr., 809 Cambridge Apts., School House Lane (44)

1950. Lynch, J. Edward, Suite 305, Wynnewood House, 300 E. Lancaster Ave., Wynnewood, Pa.
1953. Lyons, John W., 255 S. 17th St. (3)
1965. McCabe, James L., Jr., Barclay Bldg., One Belmont Ave., Bala-Cynwyd, Pa.
1932. McCahey, James F., Rittenhouse-Claridge, 18th & Walnut Sts. (3)
1965. McCarty, Daniel J., Jr., 230 N. Broad St. (19102)
1958. McClenahan, John L., 39 East Chestnut Hill Ave. (18)
1935. McClenahan, William U., 33 East Chestnut Hill Ave., Chestnut Hill (18)
1957. McConnell, Edward L., Jr., 2342 S. Broad St. (45)
1934. McCouch, Grayson P., Univ. of Pa. School of Medicine (4)
1962. McCracken, Stewart, 3701 N. Broad St. (40)
1938. McCrea, Lowrain E., 1930 Chestnut St. (3)
1958. McCune, Wallace G., 5555 Wissahickon Ave. (44)
1942. McDonald, P. Robb, Lankenau Medical Bldg. (19151)
1953. McDonnell, William V., West Jersey Hospital, Camden 4, N. J.
1952. McElroy, Robert C., 133 S. 36th St. (4)
1950. McFadden, William M., 1187 E. Washington Lane (38)
1949. McGavic, John S., 601 Montgomery Ave., Bryn Mawr, Pa.
1945. McGee, Lemuel Clyde, Hercules Powder Company, Wilmington, Del.
1954. McGehee, Edward H., 33 E. Chestnut Hill Ave. (18)
1952. McGlade, Thomas H., 719 Cooper St., Camden, N. J.
1956. McGrath, Raymond J., 1720 Spruce St. (3)
1959. McKeown, John J., Jr., 255 S. 17th St. (19103)
1933. McLaughlin, James S., 330 S. 9th St. (19107)
1966. McMichael, Harrison, 203 Medical Bldg., Univ. of Pa. (19104)
1924. McMillan, Thomas M., 1901 Walnut St. (3)
1924. McPhedran, F. Maurice, Cope House, Awbury Arboretum (19138)
1955. McStravog, Lawrence J., 6910 Market St., Upper Darby, Pa.
1954. MacFadyen, Bruce V., 1819 Pennsylvania Blvd. (3)
1943. MacFarlan, Douglas, 101 Church Rd., Ardmore, Pa.
1932. Macfarlane, Catherine, 136 S. 16th St. (2)
1964. Macht, Elmer L., Jr., York & Keith Roads, Abington, Pa.
1949. MacNeal, Perry Scott, 330 S. 9th St. (7)
1951. Mac Neish, W. J., 136 S. 16th St. (2)
1955. Macy, Dorothy, Jr., 705 Beechwood Road, Media, Pa.
1957. Madow, Leo, Woman's Medical College, 3300 Henry Ave. (19129)
1935. Maeder, LeRoy M. A., 1910 Rittenhouse Sq. (3)
1966. Maguire, Henry C., Jr., 7715 Castor Ave (19152)
1952. Mahoney, J. Francis, 250 S. 18th St. (3)
1965. Mancall, Elliott L., 230 N. Broad St. (19102)
1959. Mandel, Martin M., Benson Manor, Township Line & Washington Lane, Jenkintown, Pa.
1966. Manges, W. Bosley, 1719 Rittenhouse Sq. (19103)
1954. Manges, Willis E., Methodist Hospital, Broad & Wolf Sts. (48)
1949. Manlove, Francis R., 500 Williamson Rd., Gladwyne, Pa.
1960. Manning, Valentine R., 3336 Aldine St. (36)
1956. Manstein, George, 1351 Tabor Rd. (41)
1961. Mapow, Abraham B., 535 Pine St. (6)
1953. Marbach, A. Herbert, 1307 Tabor Rd. (41)
1948. Marden, Philip Ayer, University Hospital, 36th & Spruce Sts. (4)
1958. Marino, Daniel J., 422 East 22nd St., Chester, Pa.
1950. Marshall, E. Wayne, 907 Pine St. (19107)

1951. Martin, William L., Hahnemann Hospital (2)
1953. Marx, Halvey E., 76 Brennan Drive, Bryn Mawr, Pa.
1939. May, Hans, 255 S. 17th St. (3)
1951. Mayock, Robert L., 3600 Spruce St. (4)
1958. Mays, Ralph Whiteman, 154 W. Tulpehocken St. (44)
1961. Mechanick, Philip, 215 Clwyd Rd., Bala-Cynwyd, Pa. (19004)
1952. Mecray, Paul, Jr., 405 Loucroft Ave., Haddonfield, N. J.
1951. Medinger, Frederick G., 1941 Woodland Road, Abington, Pa.
1959. Medoff, Joseph, 5400 Wynnefield Ave. (31)
1941. Mendell, Theodore H., 2023 Spruce St. (3)
1943. Meranze, David R., 1031 Lakeside Ave. (26)
1954. Mertens-Roesler, Elizabeth, 2910 Woodpipe Lane (29)
1956. Merves, Louis, 1015 Chestnut St. (7)
1955. Mervine, Thomas B., 133 S. 36th St. (4)
1959. Metzger, Harry N., 1815 Pine St. (3)
1964. Meyer, Edward C., Fitzgerald Mercy Hospital, Darby, Pa.
1955. Meyer, Eugene A., 1438 Mt. Ephraim Ave., Camden, N. J.
1937. Meyer, George Phillip, 108 4th Ave., Haddon Hts., N. J.
1964. Michaile, Kenneth I., 1930 Chestnut St. (19103)
1956. Miller, Bernard Joseph, 6013 Greene St. (44)
1935. Miller, Ford A., 4016 Chestnut St. (4)
1939. Miller, Malcolm W., Lankenau Medical Bldg. (19151)
1939. Miller, Merle M., 6013 Greene St. (44)
1921. Miller, T. Grier, 133 S. 36th St. (4)
1955. Miller, William H., Fitzgerald Mercy Hospital, Darby, Pa.
1965. Mills, Lewis C., Hahnemann Medical College & Hospital, 230 N. Broad St. (19102)
1952. Minehart, John R., 615 E. Allegheny Ave. (19134)
1952. Mintz, S. S., 1930 Chestnut St. (3)
1963. Mishkin, Mark M., Univ. of Pa. Hospital (19104)
1950. Mitchell, John McK., Bryn Mawr Hospital, Bryn Mawr, Pa.
1952. Mitchell, Robert McNair, 807 Spruce St. (7)
1959. Mitterling, Robert C., Chestnut St. & Glendale Rd., Upper Darby, Pa.
1936. Montgomery, Hugh, 119 Glenn Road, Ardmore, Pa.
1936. Montgomery, John B., 1930 Chestnut St. (3)
1932. Montgomery, Thaddeus L., 2031 Locust St. (3)
1935. Moore, John Royal, 3401 N. Broad St. (40)
1947. Moore, Matthew Thibaud, 1813 Delancey Pl. (3)
1958. Moore, Samuel R., Jr., 1600 Arch St. (1)
1958. Morani, Alma D., 3665 Midvale Ave. (29)
1936. Morgan, David R., 218 W. Mt. Carmel Ave., Glenside, Pa.
1944. Morris, Harold H., 429 Montgomery Ave., Haverford, Pa.
1945. Morris, I. Paul, 1939 Cheltenham Ave. (17)
1965. Morse, Dryden P., 245 N. Broad St. (19107)
1964. Most, William, 994 Haddon Ave., Collingswood 7, N. J.
1957. Moyer, David G., 701 W. Main St., Lansdale, Pa.
1959. Moyer, John H., 230 N. Broad St. (2)
1941. Muckle, Craig Wright, 8016 Seminole Ave. (19118)
1929. Mudd, Stuart, Department of Bacteriology, Univ. of Pa. School of Medicine (4)
1960. Mulberger, Robert D., 1930 Chestnut St. (3)
1965. Muller, Otto, Fitzgerald-Mercy Hospital, Darby, Pa.
1930. Murphy, Douglas P., 601 S. Bowman Ave., Merion Station, Pa.

1953. Murphy, Edward J., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1958. Murphy, John J., 3600 Spruce St. (4)
1959. Murray, Edwin N., 130 N. Broadway, Camden, N. J.
1955. Murtagh, Frederick, Jr., 3401 N. Broad St. (40)
1951. Myers, David, 3701 N. Broad St. (40)
1965. Myers, Richard N., 307 Lankenau Medical Bldg. (19151)
1955. Nachod, Grace R., 5501 Greene St. (44)
1945. Naide, Meyer, 2034 Spruce St. (3)
1951. Naidoff, David, 3500 Tudor St. (36)
1966. Nance, Maurice R., 1500 Spring Garden St. (19101)
1950. Nardone, Anthony A., 912 S. 49th St. (43)
1959. Neal, Hunter, S., 406 Lankenau Medical Bldg. (19151)
1958. Nealon, Thomas F., Jr., 1025 Walnut St. (7)
1948. Neese, Paul H., 17 Derwen Road, Cynwyd, Pa.
1963. Nelson, Arthur D., 3400 N. Broad St. (40)
1936. Nelson, Guy M., 255 S. 17th St. (3)
1943. Nelson, Waldo E., 615 Moreno Rd., Narberth, Pa.
1955. Nemir, Paul, Jr., 19th & Lombard Sts. (19146)
1935. Nicholson, Jesse Thompson, 1740 Bainbridge St. (46)
1960. Nicholson, John W., III, 115 Chestnut St., Moorestown, N. J.
1947. Noone, Ernest L., 4501 Cedar Lane, Drexel Hill, Pa.
1954. Norris, Charles M., 3401 N. Broad St. (40)
1938. Norris, Robert F., 513 Wynnewood Ave., Wynnewood, Pa.
1963. Novack, Paul, 230 N. Broad St. (2)
1957. Oakey, Richard S., Jr., 309 Medical Bldg., Lankenau Hospital (51)
1963. O'Hara, A. Edward, Jefferson Medical College Hospital (19107)
1947. O'Keefe, John J., 255 South 17th St. (3)
1954. Olsen, Axel K., 230 N. Broad St. (2)
1949. O'Neill, James F., 1425 Woodland Rd., Rydal, Pa. (19046)
1954. O'Neill, Thomas, J. E., Centennial Bldg., Front St. & Lehigh Ave. (25)
1947. Ornsteen, A. M., 2007 Delancey Pl. (3)
1955. Ottenberg, Donald J., Beury Bldg., 3701 N. Broad St. (40)
1913. Outerbridge, George W., 7141 McCallum St. (19119)
1961. Owen, Barbara J., Bryn Mawr Hospital, Bryn Mawr, Pa.
1949. Padis, Nicholas, Lankenau Medical Bldg. (51)
1909. Parish, Benjamin Dores, Cresheim Arms Hotel, Allens Lane & Bryan St. (19)
1963. Parish, Benjamin D., Jr., 1201 Bethlehem Pike, Flourtown, Pa.
1945. Park, Felix Roman, 1980 Utica Sq., Tulsa, Okla.
1940. Parker, Alan P., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1948. Parkhurst, Leonard Woods, 330 S. 9th St. (7)
1952. Paxson, Newlin F., 245 N. Broad St. (7)
1932. Payne, Franklin L., Univ. of Pa. Hospital (4)
1965. Pearlstine, Beatrice, 7404 Mountain Ave. (19126)
1954. Pearce, Alexander E., 1420 Race St. (2)
1958. Pearce, Rowan C., Jr., 327 Cooper St., Camden 2, N. J.
1943. Pearson, Gerald H. J., Presidential Apts.—Adams House (31)
1954. Pearson, Manuel M., 111 N. 49th St. (39)
1952. Peck, Roy I., 3400 Spruce St. (4)
1960. Peltz, William L., 111 N. 49th St. (39)
1930. Pendergrass, Eugene P., Univ. of Pa. Hospital (4)
1953. Penneys, Raymond, University of Pennsylvania Hospital (4)
1942. Perkins, William Harvey, The Lenox, 13th & Spruce Sts. (7)

1946. Perloff, William Harry, Albert Einstein Medical Center (41)
1964. Perrin, George M., First Floor Mills Bldg., Philadelphia General Hospital, 34th & Curie Ave. (19104)
1940. Pessel, Johannes F., 224 West State St., Trenton, N. J.
1952. Peters, Michael, Fairhill Rd., Hatfield, Pa.
1961. Peterson, Lysle H., Bockus Research Institute, 19th & Lombard Sts. (19146)
1940. Pettit, Horace, 601 Suburban Sq. Bldg., Ardmore, Pa.
1949. Pettit, Mary DeWitt, 3343 W. Penn St. (29)
1946. Pfeiffer, Mildred C. J., 358 Valley Rd., Merion, Pa.
1935. Phillips, Arthur W., 3904 Walnut St. (4)
1961. Phillips, William A., Eastern Pennsylvania Psychiatric Institute (29)
1911. Piersol, George Morris, 308 Kent Rd., Wynnewood, Pa.
1948. Pierson, Daniel B., Jr., 740 Beacon Lane, Merion, Pa.
1964. Pierucci, Louis, Jr., 1025 Walnut St. (19107)
1961. Pike, Anne H., 5603 Greene St. (44)
1957. Pilling, George Platt, IV, 2600 N. Lawrence St. (33)
1933. Pillsbury, Donald M., Univ. of Pa. Hospital (4)
1957. Platt, Ruth M., 441 Lyceum Ave. (28)
1951. Poinsard, Paul J., 2031 Locust St. (3)
1937. Polk, David Stewart, Rosemont, Pa.
1956. Pontarelli, Domenic J., 1037 Great Springs Rd., Rosemont, Pa.
1953. Porreca, George A., 1912 Spruce St. (3)
1932. Porter, Roland De Lance, Abington Medical Bldg., Abington, Pa.
1951. Post, Joseph W., 1930 Chestnut St. (3)
1951. Pote, Harry H., 103 E. Ridley Ave., Ridley Park, Pa.
1958. Potter, H. Phelps, Jr., Woman's Medical College (29)
1951. Pressman, Robert S., 170 W. Olney Ave. (20)
1965. Price, Joseph J., 36 Copley Road, Upper Darby, Pa.
1947. Prickett, John A., Warrington, Bucks County, Pa.
1954. Prince, Leon N., 2025 Spruce St. (3)
1931. Pryor, Charles Allen, 255 S. 17th St. (3)
1952. Pugh, James E., 614 Church Lane, Yeadon, Pa.
1947. Putney, Floyd Johnson, 1712 Locust St. (3)
1943. Radbill, Samuel X 7043 Elmwood Ave. (42)
1953. Radbill, Sidney G., 37 S. 20th St. (3)
1966. Raffensperger, Bruce W., 8811 Germantown Ave. (19118)
1953. Raffensperger, Edward C., 260 St. James Place (6)
1945. Rakoff, Abraham Edward, 269 S. 19th St. (3)
1953. Ralston, Edgar L., 3400 Spruce St. (4)
1931. Ramsey, Frank M., 620 E. Willow Grove Ave. (18)
1953. Ranieri, Tito A., 2320 S. Broad St. (45)
1941. Rankin, Charles A., Ludlow & Heather Rd., Upper Darby, Pa.
1951. Rathmell, Thomas K., 446 Bellevue Ave., Trenton, N. J.
1926. Ravdin, I. S., Univ. of Pa. Hospital (4)
1956. Ravdin, Robert Glenn, 3400 Spruce St. (4)
1959. Raventos, Antolin, 3400 Spruce St. (4)
1962. Raymond, F. Douglas, Jr., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1964. Raymond, Samuel, 711 Maloney Bldg., University Hospital, 36th & Spruce Sts. (19104)
1961. Read, William T., Jr., 110 Munn Lane, Cherry Hill, N. J. (08034)
1954. Reagan, Lindley B., 175 Madison Ave., Mt. Holly, N. J.
1965. Reddy, John B., 1025 Walnut St. (19107)

1960. Reed, Theodore P., Lankenau Medical Bldg. (19151)
1928. Reese, Warren S., 2118 Locust St. (3)
1919. Reimann, Stanley P., 703 W. Phil-Ellena St. (19)
1964. Reinhard, John J., Jr., 335 Woodstown Road, Salem, N. J.
1956. Reishtein, William A., 16 Blancoyd Rd., Merion Station, Pa.
1963. Reisinger, Paul B., 855 Berkeley Ave., Trenton, N. J.
1951. Rentschler, Laurence B., 5800 Ridge Ave. (28)
1945. Rhoads, Jonathan E., Univ. of Pa. Hospital (4)
1964. Rhoads, Rebecca M. P., 104 Station Ave., Westville, N. J.
1964. Rhoads, S. Creadick, 104 Station Ave., Westville, N. J.
1963. Rial, William Y., 111 Dartmouth Ave., Swarthmore, Pa.
1951. Richardson, Fred Mac D., 160 Carpenter Lane (19)
1919. Richardson, Russell, Shamona Mill, Downingtown, Pa.
1942. Riggs, Helena E., 150 Hewitt Rd., Wyncote, Pa.
1936. Ritter, Joseph A., 1034 Bryn Mawr Ave., Narberth, Pa.
1932. Robbins, Frederick R., 317 Milbank Rd., Bryn Mawr, Pa.
1952. Robbins, Robert, 3401 N. Broad St. (40)
1960. Robbins, William S., The Iroquois, Suite 1303, City Line & 47th St. (19131)
1954. Roberts, Brooke, 3400 Spruce St. (4)
1957. Roberts, Joan Mary, 4 W. Mt. Pleasant Ave. (19)
1932. Robertson, Harold F., 2118 Pine St. (3)
1964. Robinson, James H., 5900 Spruce St. (19139)
1938. Roche, Philip Q., The Towers, Stenton Ave. & Mermaid Lane (19118)
1960. Roeders, Paul H., 330 S. 9th St. (7)
1955. Rogers, Fred B., 3401 N. Broad St. (40)
1951. Ronis, Bernard J., 2106 Spruce St. (3)
1948. Roscoe, Constantine R., 7226 Castor Ave. (24)
1928. Rose, Edward, 426 Owen Rd., Wynnewood, Pa.
1936. Rose, Elizabeth Kirk, 426 Owen Rd., Wynnewood, Pa.
1959. Rose, Isadore, 6000 W. Oxford St. (19151)
1952. Rose, S. Brandt, Chestnut Hill Hospital (18)
1965. Rosenberg, Hyman, 1555 Haddon Ave., Camden, N. J.
1966. Rosenberg, Morton, 1025 Walnut St. (19107)
1946. Rosemond, George Parrott, 3401 N. Broad St. (40)
1960. Rosenow, Edward C., Jr., American College of Physicians, 4200 Pine St. (4)
1948. Rothman, Maurice M., 1727 Spruce St. (3)
1951. Rouse, George P., Jr., 250 South 18th St. (2)
1963. Rovit, Richard L., Jefferson Medical College (7)
1965. Rowe, Daniel S., Irvine Bldg., Narberth & Montgomery Aves., Narberth, Pa.
1952. Roxby, Bruce S., 5501 Greene St. (44)
1955. Roxby, John B., Jr., 4821 Germantown Ave. (44)
1949. Royster, Henry P., 3400 Spruce St. (4)
1941. Royster, Hubert A., Jr., 888 Glenbrook Ave., Bryn Mawr, Pa.
1959. Rubin, Alan, 255 S. 17th St. (3)
1952. Rubin, I. Edward, 255 S. 17th St. (3)
1933. Rudolphy, Jay Besson, 37 S. 20th St. (19103)
1946. Rupp, Charles, 133 S. 36th St. (4)
1947. Rush, Alexander, 330 S. 9th St. (7)
1963. Rutter, William A., 425 Wister Rd., Wynnewood, Pa.
1963. Ryan, James J., 301 E. City Line, Bala-Cynwyd, Pa.
1945. Rynes, Samuel E., 334 S. 21st St. (3)
1965. Sachs, Marvin L., 133 S. 36th St. (19104)

1952. Sain, Fletcher D., Abington Medical Bldg., York & Keith Rds., Abington, Pa.
1958. Sall, Manuel, 255 S. 17th St. (3)
1952. Salner, Nathan P., 6812 Castor Ave. (24)
1952. Saltzman, Maurice, 2037 Spruce St. (3)
1944. Sampson, David Alan, 726 Braeburn Lane, Penn Valley, Narberth, Pa.
1964. Santangelo, Samuel C., 1941 Woodland Road, Abington, Pa.
1950. Sarner, Joseph B., 289 Locust St. (19106)
1949. Saul, Leon J., Highland Ave., Media, Pa.
1908. Sautter, Albert C., 6733 Emlen St. (19)
1954. Savacool, J. Woodrow, 146 W. Tulpehocken St. (44)
1947. Sayen, John J., 3600 Spruce St. (4)
1948. Scarano, Joseph Albert, 1432 S. Broad St. (46)
1917. Schaeffer, J. Parsons, 4634 Spruce St. (39)
1929. Scheffey, Lewis C., 601 Walnut Lane, Haverford, Pa.
1942. Schfie, Harold G., 3400 Spruce St. (4)
1929. Schenck, Harry P., 1235 Wyngate Rd., Wynnewood, Pa.
1945. Schlezinger, Nathan S., 255 S. 17th St. (3)
1961. Schlosser, Woodrow D., 3701 N. Broad St. (40)
1917. Schnabel, Truman G., 1704 Pine St. (3)
1958. Schnabel, Truman G., Jr., Phila. General Hospital (4)
1957. Schnall, Nathan, 2037 Pine St. (3)
1962. Schneider, Henry C., 4801 Penn St. (24)
1955. Schreader, Charles J., 318 W. Godfrey Ave. (20)
1958. Schreck, Kenneth M., Temple University School of Medicine (40)
1952. Schulz, Norbert J., 1901 Walnut St. (3)
1963. Schumacher, L. Richard, 60 E. Court St., Doylestown, Pa.
1950. Schumann, Francis, 8811 Germantown Ave. (18)
1948. Schwarz, Gabriel A., 133 S. 36th St. (4)
1962. Schwarz, Henry P., Philadelphia General Hospital (4)
1955. Schwegman, Cletus W., Hospital of the University of Penna. (4)
1966. Scott, J. Clifford, 826 Maple Ave., Berwyn, Pa.
1930. Scott, John Porter, Children's Hospital, 1740 Bainbridge St. (46)
1950. Scott, Michael, 3401 N. Broad St. (40)
1940. Scott, T. F. McNair, Children's Hospital, 1740 Bainbridge St. (46)
1952. Seifer, Arthur F., 710 South Main St., Phoenixville, Pa.
1958. Sellers, Alfred M., Hosp. of the Univ. of Pa. (4)
1952. Semisch, Charles W., III, 1344 Gilbert Rd., Meadowbrook, Pa.
1966. Shaffer, Horace M., 208 W. State St., Trenton, N. J. (08608)
1960. Shannon, Gerard M., 8118 Bustleton Ave. (15)
1950. Sharp, Reuben L., 719 Cooper St., Camden, N. J.
1963. Sharples, Wynne, 454 S. Ithan Ave., Villanova, Pa. (19085)
1928. Sharpless, Frederick C., 621 Railroad Ave., Haverford, Pa.
1956. Shaw, Daniel L., Jr., 702 Knox Rd., Villanova, Pa.
1963. Shearburn, Edwin W., 306 Lankenau Medical Bldg. (19151)
1955. Schechter, Fred R., 2461 No. 54th St. (31)
1954. Shelley, Walter B., 36th & Spruce Sts. (4)
1955. Shenkin, Henry A., Episcopal Hospital (25)
1946. Shepherd, Samuel Garfield, 2039 Pine St. (3)
1932. Sheridan, Joyce T., 412 W. Durham St. (19)
1956. Sherson, Jacob S., 131 Channing Ave., Malvern, Pa.
1964. Shimkin, Michael B., Temple University School of Medicine (19140)
1936. Shipman, James Shelby, 514 Cooper St., Camden, N. J.

1958. Shipps, Hammell P., 719 Cooper St., Camden, N. J. (2)
1957. Shope, Edward Pierce Lentz, 807 Wilson Bldg., Camden, N. J.
1946. Shoup, George Daniel, 121 W. Walnut Lane (44)
1955. Shubin, Harry, 6601 N. 21st St. (38)
1952. Shuman, Charles R., 3401 N. Broad St. (40)
1949. Sidlick, David M., 255 S. 17th St. (3)
1941. Silcox, Louis E., Lankenau Medical Bldg. (19151)
1956. Sillars, Charles H., Abington Memorial Hospital, Abington, Pa.
1963. Silverman, Daniel, 269 South 19th St. (19103)
1955. Silverstein, Alexander, 2114 Pine St. (3)
1961. Simmons, Vaughan P., The Fidelity Mutual Life Insurance Co. (1)
1954. Singmaster, Lawrence, 272 Cheswold Lane, Haverford, Pa.
1952. Skromak, Stanley J., 5108 Torresdale Ave. (24)
1929. Smith, Austin T., 330 S. 9th St. (7)
1964. Smith, Edgar C., 7100 Marshall Road, Upper Darby, Pa.
1965. Smith, Eleanor M., 3300 Henry Ave. (19129)
1955. Smith, J. Winslow, 3034 Darby Rd., Ardmore, Pa.
1933. Smith, Lauren Howe, 111 N. 49th St. (39)
1952. Smith, Richard T., 330 S. 49th St. (7)
1964. Smyth, Murray G., Jr., Smith Kline Instrument Co., 1500 Spring Garden St. (19101)
1951. Snape, William J., 573 Stevens St., Camden, N. J.
1938. Snodgrass, L. E., Barclay Hotel, 18th & Rittenhouse Sq. (3)
1953. Snyder, G. Gordon, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1958. Sodeman, William A., 1025 Walnut St. (7)
1961. Soffe, Alvin M., 1930 Chestnut St. (3)
1935. Sokoloff, Martin J., 255 S. 17th St. (3)
1964. Soll, David B., 5001 Frankford Ave. (19124)
1940. Soloff, Louis A., 3401 N. Broad St. (40)
1950. Somerville, William J., 37 S. 20th St. (3)
1944. Sommer, George N. J., Jr., 120 W. State St., Trenton, N. J.
1952. Sones, Maurice, Mt. Airy Medical Bldg. (19)
1951. Sonneborn, Duane G., 1200 W. Erie Ave. (24)
1928. Spaeth, Edmund B., 1930 Chestnut St. (3)
1958. Spaeth, Philip G., 1930 Chestnut St. (3)
1937. Spangler, John Luther, Devon, Pa.
1957. Spelman, Joseph Worcester, Dept. of Public Health, 13th & Wood Sts. (7)
1935. Spiegel, Ernest A., 6807 Lawnton Ave. (26)
1961. Spiegelman, Jay, Benson East Apt., Jenkintown, Pa.
1955. Spitz, Eugene B., 40–50 W. Front St., Media, Pa.
1958. Splendido, Joseph A., 608 W. Cliveden (19)
1961. Stahlgren, LeRoy H., 419 South 19th St. (46)
1960. Stainback, William C., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1957. Stanley, Robert C. G., 2315 Edgemont Rd., Chester, Pa.
1927. Starr, Isaac, 505 Cresheim Valley Rd. (18)
1952. Stauffer, Herbert M., 3401 N. Broad St. (40)
1952. Stayman, Joseph W., Jr., 8815 Germantown Ave. (18)
1945. Stecher, H. Armin, 1510 Darby Rd., Havertown, Pa.
1955. Steel, Howard H., 238 W. Allens Lane (19119)
1952. Steiger, William A., 3401 N. Broad St. (40)
1964. Stein, Donald B., Jr., Fitzgerald Mercy Hospital, Darby, Pa.
1946. Stein, Irvin, 1936 Spruce St. (3)

1953. Stein, Raymond O., 269 S. 19th St. (3)
1966. Stein, Samuel C., 1930 Chestnut St. (19103)
1963. Steinberg, Stanley B., 2461 N. 54th St. (19131)
1936. Steinfield, Edward, 2200 Benjamin Franklin Parkway (30)
1951. Sterling, Julian A., 1008 Sharpless Rd. (26)
1948. Stevens, Lloyd W., 133 S. 36th St. (4)
1928. Stokes, Joseph, Jr., Henry Phipps Institute, 4219 Chester Ave. (19104)
1943. Stokes, S. Emlen, 129 Chester Ave., Moorestown, N. J.
1954. Stone, Hrant H., E. Shawmont Ave. (28)
1961. Strang, John E., 330 S. 9th St. (7)
1953. Strawbridge, Rendall R., Lankenau Medical Bldg. (19151)
1937. Strumia, Max M., Penn Valley, Narberth, Pa.
1960. Strumia, Paul V., Bryn Mawr Hospital, Bryn Mawr, Pa.
1951. Sturgis, Katharine Boucot, Women's Medical College, Henry Ave. & Abbotsford Road (19129)
1927. Sturgis, Samuel Booth, 349 Wistar Rd., Wynnewood, Pa.
1930. Sunderman, F. William, 1833 Delancey Place (3)
1966. Sullivan, Howard E., Jr., Bryn Mawr Medical Bldg., Bryn Mawr, Pa. (19010)
1954. Sussman, Marcel S., 101 S. 20th St. (3)
1963. Sutliff, Frederick P., 3701 N. Broad St. (19140)
1965. Sutnick, Alton I., 2135 St. James Place (19103)
1965. Swartley, Robert N., 8815 Germantown Ave. (19118)
1952. Sweeney, Francis X., Station A, Marlboro, N. J. (07746)
1952. Talbot, Timothy R., Jr., 204 Booth Lane, Haverford, Pa.
1943. Tassman, Isaac S., 2601 Parkway (19130)
1963. Tassman, William S., 626 Four Penn Center Plaza, 16th & J. F. Kennedy Blvd. (19102)
1946. Tauber, Robert, 2019 Walnut St. (3)
1952. Taylor, Ann Gray, 6364 Germantown Ave. (44)
1960. Taylor, Daniel B., 2241 Federal St. (46)
1965. Taylor, Richard C., 11th & Sansom Sts. (19107)
1956. Templeton, John Y., III, 805 Spruce St. (19107)
1951. Theodos, Peter A., 1930 Chestnut St. (3)
1961. Therman, Per-Olof, 111 N. 49th St. (39)
1959. Thomas, Arthur H., 5240 Vine St. (39)
1946. Thomas, Carmen C., 1930 Chestnut St. (3)
1964. Thomas, John W., 5900 Spruce St. (19139)
1952. Thompson, Charles M., 255 S. 17th St. (3)
1927. Thorington, J. Monroe, Cambridge Apts., Wissahickon Ave. & School House Lane (44)
1936. Thudium, William J., 700 Merion Square Rd., Gladwyne, Pa.
1954. Tindall, Dorothy D., 1930 Rittenhouse Sq. (3)
1935. Toland, Owen J., 336 Aubrey Rd., Wynnewood, Pa.
1952. Tondreau, Roderick L., 523 Old Gulph Rd., Bryn Mawr, Pa.
1949. Tornay, Anthony S., 2038 Locust St. (3)
1966. Torrance, Edward G., 678 Burmont Rd., Drexel Hill, Pa.
1936. Towson, Charles Emory, 224 W. Washington Lane (44)
1955. Trimpi, Howard D., 501 N. 17th St., Allentown, Pa.
1954. Trommer, Philip R., 258 S. 18th St. (3)
1956. Troncelliti, Mario V., Pennsylvania Hospital (7)
1953. Tropea, Frank, Jr., 500 Mulberry Lane, Haverford, Pa.
1947. Trueman, Robert H., 2101 Chestnut St. (3)

1954. Truitt, R. Marshall, Jr., 740 Westview St. (19)
1965. Tsaltas, Theodore T., 1025 Walnut St. (19107)
1966. Tucker, Gabriel F., Jr., 3401 N. Broad St. (19140)
1959. Tuddenham, William J., Pennsylvania Hospital (7)
1938. Tuft, Louis, 1530 Locust St. (2)
1964. Tulsky, Emanuel G., Abington Memorial Hospital, Abington, Pa. (19001)
1933. Tumen, Henry J., 1830 Rittenhouse Square (3)
1938. Turman, Christopher M., 1245 Highland Ave., Abington, Pa. (19001)
1923. Turner, Creighton H., 1731 Pine St. (3)
1954. Turner, Linton W., 3401 N. Broad St. (40)
1959. Tyson, R. Robert, 3401 N. Broad St. (40)
1937. Uhle, Charles A. W., Lankenau Medical Bldg. (19151)
1953. Ulin, Alexander W., 230 N. Broad St. (2)
1960. Uricchio, Joseph F., 245 N. Broad St. (7)
1950. Valdes-Dapena, Antonio, 214 Plush Mill Rd., Wallingford, Pa.
1958. Van den Noort, Gordon S., 888 Glenbrook Ave., Bryn Mawr, Pa.
1937. Vander Veer, Joseph B., 330 S. 9th St. (7)
1937. Van Loon, Emily Lois, 255 S. 17th St. (3)
1960. Van Meter, Ralph H., 244 W. Main St., Moorestown, N. J.
1933. Vastine, Jacob H., 2nd, 267 Kent Rd., Wynnewood, Pa.
1963. Vaughn, Arthur R., Jr., 512 W. Erie Ave. (19140)
1958. Velkoff, Cyril L., 2100 Walnut St. (3)
1965. Viggiano, Louis X., 301 Long Lane, Upper Darby, Pa.
1952. Vischer, Thomas J., 5903 Greene St. (44)
1940. Voegelin, Adrian W., Germantown Professional Bldg. (44)
1960. Wagenheim, Harry H., 1822 Spruce St. (3)
1949. Wagner, Frederick B., Jr., 800 Chauncy Road, Narberth, Pa.
1949. Wagner, Joseph A., 201 Highland Ave., Bryn Mawr, Pa.
1938. Waldman, Joseph, 404 Meadowbrook Lane (18)
1955. Waldron, Jerome M., Evergreen Towers, 8900 Roosevelt Blvd. (19115)
1932. Walkling, Adolph A., 330 S. 9th St. (19107)
1956. Watkins, E. Lloyd, 8811 Germantown Ave. (18)
1954. Waugh, Elizabeth S., 348 Green Lane (28)
1952. Weaver, Harry S., Jr., 37 S. 20th St. (3)
1955. Weaver, Robert L., Chetwynd Apts., 1030 E. Lancaster Ave., Rosemont, Pa. (19010)
1953. Weber, Lennard L., 255 S. 17th St. (19151)
1930. Weeder, S. Dana, The Stafford House, Chelten & Wissahickon Aves. (44)
1952. Weinstein, George L., 255 S. 17th St. (3)
1950. Weiss, Sidney, 2037 Locust St. (3)
1965. Weiss, William, Philadelphia General Hospital, 34th & Curie Ave. (19104)
1959. Wellenbach, Burton L., 1930 Chestnut St. (19103)
1951. Welty, Jack W., Montgomery Ave. & Owen Rd., Wynnewood, Pa.
1955. Wendkos, Martin H., Green Hill in Lower Merion (19151)
1962. Wentz, Clarkson, 20 S. Valley Road, Paoli, Pa.
1961. Wermuth, William C., 111 N. 49th St. (39)
1959. West, Clifton F., Jr., 406 Lankenau Medical Bldg. (19151)
1921. Whitaker, William, 4645 Oakland St. (24)
1936. White, Ellen Pawling Corson-, Gladwyne, Pa.
1965. White, Joseph C., 1025 Walnut St. (19107)
1960. Whiteley, William H., 1015 Chestnut St. (7)
1925. Widmann, Bernard P., 250 S. 18th St. (3)

1954. Wieder, Henry S., Jr., 330 S. 9th St. (7)
1939. Willauer, George, 6129 Greene St. (44)
1937. Williams, John C., 6370 Germantown Ave. (44)
1965. Williams, Kirkley, R., Bryn Mawr Medical Bldg., Bryn Mawr, Pa. (19010)
1920. Williams, Philip F., 256 Broughton Lane, Villanova, Pa.
1950. Williams, R. G., Univ. of Pa. School of Medicine (4)
1927. Williamson, Ernest G., 6353 Woodbine Ave. (19151)
1945. Wilson, John F., 2013 Delancey Pl. (3)
1949. Wilson, William W., 133 S. 36th St. (4)
1957. Winkelman, N. William, Jr., 4141 Apalogen Rd. (44)
1963. Winston, Joseph M., Jeanes Hospital (11)
1941. Wirts, C. Wilmer, 2017 Delancey St. (3)
1966. Wise, John S., 433 Bellevue Ave., Trenton, N. J. (08618)
1961. Wise, Robert L., 1025 Walnut St. (7)
1953. Wohl, George T., Philadelphia General Hospital (4)
1933. Wohl, Michael G., 1727 Pine St. (3)
1958. Woldow, Irving, Einstein Med. Center, York & Tabor Rds. (41)
1958. Wolf, John H., 124 W. Walnut Lane (44)
1944. Wolf, Lewis R., 3474 Frankford Ave. (34)
1962. Wolferth, Charles C., Jr., 230 N. Broad St. (2)
1964. Wolfson, Robert J., 3701 N. Broad St. (19140)
1964. Wolgin, William, 2104 Delancey Place (19103)
1957. Wolkowicz, Michael I., 2022 Spruce St. (3)
1942. Wolman, Irving J., 7607 Woodlawn Ave. (26)
1966. Wood, Alfred C., Jr., 6386 Church Rd. (19151)
1932. Wood, Francis C., 3400 Spruce St. (19104)
1944. Wood, H. Curtis, Jr., 7010 Lafayette Ave., Fort Washington, Pa.
1966. Wood, Margaret G., 3400 Spruce St. (19104)
1953. Woodruff, Marston T., 4940 Penn St. (24)
1928. Wright, Carroll S., 1402 Spruce St. (2)
1960. Wurzel, Harold A., 3400 Spruce St. (4)
1966. Yaskin, H. Edward, 589 Stevens St., Camden, N. J. (08103)
1964. Young, Alma L., 3343 W. Penn St. (19129)
1941. Young, Barton R., Germantown Hospital (44)
1961. Zanni, Anthony L., 111 N. 49th St. (39)
1957. Zaslow, Jerry, 1351 Tabor Rd. (41)
1955. Zatuchni, Jacob, 3401 N. Broad St. (40)
1946. Zeigerman, Joseph H., 2105 Spruce St. (3)
1949. Zintl, William J., 69th & Market Sts., Upper Darby, Pa.
1956. Ziserman, Abraham J., 2046 Pine St. (3)
1962. Zubrow, Sidney N., 521 Pine St. (6)
1933. Zulick, J. Donald, 307 Fisher Rd., Jenkintown, Pa. (19046)
1965. Zweiman, Burton, Univ. of Pa. Hospital (19104)

Non-Resident Fellows

ELECTED

1936. Alexander, Fay K., Lincolnville, Maine
1953. Allman, David B., 104 St. Charles Place, Atlantic City, N. J.
1941. *Aronson, Ronald S., 9401 Byeforde Road, Kensington, Md.

* Military Service.

1954. Austin, George M., University of Oregon Medical School, Portland, Oregon
1942. Bachman, Carl, Rutherford, Napa Co., Calif.
1958. Ballinger, Walter F., II, Johns Hopkins Hospital, 1900 E. Monument Ave., Baltimore, Md. (21205)
1931. Bates, William, Harrisburg Hospital, Harrisburg, Pa.
1955. Beckfield, William J., Luther Hospital, 310 Chestnut St., Eau Claire, Wisconsin
1949. Beecham, Clayton T., Geisinger Medical Center, Danville, Pa.
1932. Behney, Charles A., P. O. Box 4256, San Jose Branch, Bisbee, Arizona
1955. Blank, Harvey, Jackson Memorial Hospital, Miami 36, Fla.
1921. Borzell, Francis F., R. D. 2, Box 2051, Browns Mills, N. J.
1937. Braceland, Francis J., The Institute of Living, 200 Retreat Ave., Hartford, Conn.
1951. Brinton, S. Jervis, Box 3, Avalon, N. J.
1948. *Brown, Robert B., U. S. Naval Hospital, Bethesda, Md.
1959. Browneller, Ellsworth R., Geisinger Medical Center, Danville, Pa.
1953. Burbidge, J. Raymond, 163 Nassau St., Princeton, N. J.
1952. Bumgardner, Heath D., 13 S. Main St., Cape May Court House, N. J.
1948. Chapman, John P., Calle Fray Junipero Serra 26, Palma de Mallorca, Balearic Islands, Spain
1950. Chapple, Charles C., 2612 Naylor Rd., S.E., Washington 20020 D. C.
1941. Chieleden, John, 1012 Volusia Ave., Daytona Beach, Fla.
1930. Clarke, Francis Mann, 116 New St., New Brunswick, N. J.
1926. Clerf, Louis H., 5575-8th Ave., North St. Petersburg, Fla.
1964. Cohen, Sheldon G., 309 S. Franklin St., Wilkes-Barre, Pa.
1930. Cottrell, James E., 27 Shinnecock Trail, Medford Lakes, N. J.
1960. Cowley, Allen W., Sr., 1919 N. Front St., Harrisburg, Pa.
1947. Cutler, Norman L., 1300 Harrison St., Wilmington, Del.
1941. *Cuttle, Tracy D., U. S. Naval Hospital, Chelsea, Mass. (02150)
1959. Dannenberg, Arthur M., Jr., Johns Hopkins School of Hygiene, 615 N. Wolfe St., Baltimore, Md. (21205)
1955. Daugherty, J. Arthur, 1511 N. Front St., Harrisburg, Pa.
1937. Davis, Perk Lee, Turkey Hollow, R. D. 5, Waynesburg, Pa. (15370)
1954. Deitrick, John E., Cornell Univ. Medical College, 1300 York Ave., New York 21, N. Y.
1941. Dixon, Harold M., 4805 46th St., N.W., Washington 16, D. C.
1953. Dixon, James P., Antioch College, Yellow Springs, Ohio
1961. Duane, Thomas D., 35 E. Elizabeth Ave., Bethlehem, Pa.
1959. Durgin, Bernice Elise, 221 N. Allegheny St., Bellefont, Pa.
1947. Durkin, John K., V.A. Hospital, Coatesville, Pa. (19320)
1964. Eckenhoff, James E., Northwestern Univ. Medical School, Chicago, Ill. (60611)
1955. Edwards, Margaret Hay, 800 4th St., S.W., Washington 24, D. C.
1953. Eisenberg, Isadore J., 2806 Green St., Harrisburg, Pa.
1951. Ellis, Mackinnon, V.A. Hospital Martinez, Cal.
1957. *Errion, Arthur Robbins, U. S. Naval Hospital, Fleet Post Office, San Francisco, Cal. (96662)
1951. Ervin, Carl E., 240 North Third Street, Harrisburg, Pa.
1944. Estes, W. L., Jr., 35 E. Elizabeth Ave., Bethlehem, Pa.
1954. Evans, Harry D., Jr., American Cyanamid Co., 1 Caspar St., Danbury, Conn.
1952. Faller, Constantine P., 127 State St., Harrisburg, Pa.
1952. Flinn, Lewis B., 1306 Broom St., Wilmington 6, Del.
1940. Forrester, James S., Harrisburg Polyclinic Hospital, Harrisburg, Pa.

* Military Service.

1951. Friedland, Carl K., 271 W. Blackwell St., Dover, N. J.
1947. Gaskill, Herbert S., 9648 E. Powers Drive, Englewood, Colo.
1913. Gates, Nathaniel, 10 Peterboro Ave., Detroit, Mich.
1958. Geckeler, George D., Tranquility, S. Windham, Vt.
1957. Giering, John Fleming, 84 James St., Kingston, Pa.
1931. Gilman, Robert Louis, Cheyney, Pa.
1954. Godfrey, Ellwood W., Princeton Hospital, Princeton, N. J.
1928. Gordon, Burgess L., 1550 Lake Shore Dr., Chicago, Illinois
1952. Grieco, Reynold M., 2 W. 4th St., Williamsport, Pa.
1934. Griffith, John Q., Jr., 6 North Fredericksburg Ave., Margate, N. J.
1952. Gross, Elmer R., Medical Arts Bldg., Wilmington, Del.
1933. Gruber, Charles M., 1313 College Ave., Redlands, Calif.
1951. Hafkenschiel, Joseph H., Jr., 450 Sutter St., San Francisco, Cal. (94108)
1935. Haines, Harlan F., 231 N. Pine St., Seaford, Del.
1939. Hamblock, Leonard C., Masonic Homes, Elizabethtown, Pa. (17022)
1955. Harris, John H., 1301-A N. Second St., Harrisburg, Pa.
1932. Harris, Stanley E., 229 Maple Ave., Delanco, N. J.
1936. Hatch, Lerleen Clement, 1642 Saddle Hill Drive, Logan, Utah
1947. Hawthorne, Herbert R., 1016 Yardley Rd., Morrisville, Pa.
1928. Hayman, Joseph M., Jr., Tufts University Medical School, Boston, Mass.
1946. Hendrickson, Frank O., Jupiter, Fla.
1944. Hershey, J. Ivan, V.A. Hospital, Shreveport, La.
1955. Hills, Arthur G., 1000 N. W. 17th St., Miami, Fla. (36)
1933. Hitzrot, Lewis H., 161 Patton Ave., Princeton, N. J. (08540)
1950. Horn, Robert C., Henry Ford Hospital, Detroit, Mich.
1953. Imber, Irving, 428 Walnut St., Reading, Pa.
1958. Impink, Robert R., 405 Oley St., Reading, Pa.
1935. Ingleby, Helen, The Church House, Heacham, King's Lynn, England
1921. Ivy, Robert H., 104 Dalton Rd., Paoli, Pa.
1960. Jenson, William K., 715 Sheridan Ave., Cody, Wyoming
1955. Jordan, Charlotte B., 175 E. Brown St., E. Stroudsburg, Pa.
1955. Jordan, Claus G., 175 E. Brown St., E. Stroudsburg, Pa.
1936. Kain, Thomas M., 30 Northeast 97th St., Miami, Fla.
1956. Keffer, William H., 413 Oley St., Reading, Pa.
1947. Kelchner, Clyde H., 1125 Turner St., Allentown, Pa.
1944. LaMotte, William O., Plaza Apts., 1303 Delaware Ave., Wilmington, Del. (19806)
1954. LaMotte, William O., Jr., Professional Bldg., Wilmington 3, Del.
1936. Leaman, William G., Jr., P. O. Box 463, Unionville, Pa. (19375)
1943. Leopold, Irving H., The Mount Sinai Hospital, 100th St. & 5th Ave., New York, N. Y. (10029)
1952. Levan, John B., 401 Oley St., Reading, Pa.
1960. Lewis, David H., Hogenskildsgatan 13, Göteborg Ö, Sweden
1949. Lhamon, William T., The New York Hospital, 525 E. 68th St., New York, N. Y. (10021)
1954. Light, John J. B., 25 N. 9th St., Lebanon, Pa.
1954. Lindenmuth, Woodrow W., V.A. Hospital, West Haven, Conn.
1948. Livingood, Clarence S., Henry Ford Hospital, Detroit 2, Mich.
1933. Long, Esmond R., Conifer, Pedlar Mills, Va.
1962. McGregor, Robert A., The Professional Bldg., Augustine Cut-Off, Wilmington 3, Del.
1948. McLaughlin, John T., 655 N. Central Ave., Glendale, Calif.

1950. Mackmull, Gulden, 174 Nob Hill Lane, Ventura, California
1942. Manges, Lewis C., Jr., Read Memorial Hospital, Hancock, N. Y.
1959. Maniglia, Rosario, Holy Spirit Hospital, Camp Hill, Pa.
1953. Margolies, Michael, 567 E. Chestnut St., Coatesville, Pa.
1955. Margolies, M. Price, 379 E. Chestnut St., Coatesville, Pa.
1935. Mason, James B., 1730 S. Jackson St., Tacoma, Washington
1932. Meade, Richard H., Jr., 750 San Jose Dr., Grand Rapids, Mich.
1936. Middleton, William Shainline, 2114 Adams St., Madison, Wisc.
1946. Miller, Franklin R., Snyder-Jones Clinic, First Nat. Bk. Bldg., Winfield, Kansas
1949. Motley, Hurley L., 1212 Shatto St., Los Angeles, Calif.
1949. Mulholland, Stanford W., P.O. Box C, Christiansted, St. Croix, Virgin Islands (00820)
1937. Nicholson, Samuel T., 2nd, 642 High St., Pottstown, Pa.
1960. Ojers, Gaylord W., 35 E. Elizabeth Ave., Bethlehem, Pa.
1956. Oppenheimer, Albert, 224 E. Main St., Moorestown, N. J.
1926. Paul, John Rodman, 333 Cedar St., New Haven, Conn.
1959. Pendergrass, Henry P., Massachusetts General Hospital, Boston, Mass.
1950. Pincus, Irwin J., 610 N. Roxbury Drive, Beverly Hills, Calif.
1958. Rachlin, Lillian, 370 Golden Oak Drive, Portola Valley, Calif. (94026)
1938. Read, Hilton S., 5407 Atlantic Ave., Atlantic City, N. J.
1964. Reed, Miriam, 253 Witherspoon St., Princeton, N. J.
1958. Reinhardt, David J., III, 1303 Delaware Ave., Wilmington, Del.
1936. Reisinger, John A., 1835 Eye St., N.W., Washington, D. C.
1955. Rettew, Philip L., 612 Museum Rd., Reading, Pa.
1961. Richardson, Herschel E., 205 Mayerline St., Houston, Texas
1961. Rodahl, Kaare, Director, Institute for Work Physiology, Gydas Vei 8, Oslo, Norway
1947. Rogers, Arthur Merriam, 1351 Durwood Drive, Charlotte, N. C.
1954. Sampson, Martin C., Wallace Laboratories, Cranbury, N. J.
1936. Sands, Joseph Evans, 135 107th St., Stone Harbor, N. J.
1945. Schell, James F., 506 Sharpley Lane, Wilmington, Del.
1921. Schumann, Edward A., 4141 Jackson Drive, Lafayette Hill, Pa.
1951. Seitchik, Joseph, Sinai Hospital of Baltimore, Baltimore, Md.
1941. Shands, Alfred R., Jr., Alfred I. duPont Institute, P.O. Box 269, Wilmington, Del. (19899)
1964. Sharpe, William D., New Jersey College of Medicine, Jersey City 4, N. J.
1950. Shiffer, Paul H., Dreher Ave., R.D. #2, Stroudsburg, Pa.
1951. Shorey, Winston K., 7117 Shamrock Drive, Little Rock, Arkansas
1933. Smelzer, Donald C., 207 E. Orange St., Lancaster, Pa.
1954. Smith, Charles W., 128 State St., Harrisburg, Pa.
1927. Smyth, Calvin M., Hartsville, Bucks Co., Pa. (18974)
1929. Sponsler, Marshall B., 103 Lansdowne Road, DeWitt, N. Y.
1942. Stengel, Alfred, Jr., Maple Ave., Katonah, N. Y.
1955. Stevenson, Theodore D., 475 Riverside Drive, New York, N. Y. (10027)
1934. Stewart, Sloan G., 6200 Atlantic Ave., Ventnor, N. J.
1931. Stiles, Merritt H., E. 406 14th Ave., Spokane 3, Wash.
1953. Stroud, Morris W., 3rd, Harvard Rd., Cleveland, Ohio
1934. Summey, Thomas J., Morrowdale Farm, Rt. 2, Charlottesville, Va.
1961. Sunderman, F. William, Jr., University of Florida College of Medicine, Gainesville, Fla. (32603)
1931. Taylor, Norman H., Queen of the East, E. Broadway, Hamilton, Bermuda

1928. Thomas, J. Earl, Loma Linda University, Loma Linda, Calif.
1942. Thompson, Wesley D., 247 E. 3rd St., Lewistown, Pa.
1941. Tompkins, Pendleton, 490 Post St., San Francisco, Calif.
1959. Toole, James F., Bowman Gray School of Medicine, Winston Salem, N. C.
1897. Veasey, Clarence A., 1118 W. 9th Ave., Spokane 9, Wash.
1941. Weaver, Ruth H., 108 Atlantic Ave., Atlantic City, N. J.
1957. Webster, Marie, 1623 Hyde St., San Francisco 9, California
1959. Whayne, Tom F., University of Kentucky Medical Center, Lexington, Ky.
1966. White, Richard K., 1702 Walnut St., Allentown, Pa. (18104)
1936. Wilder, Theodore S., Linden Lane, Sherborn, Mass.
1935. Willard, John H., Harlan Memorial Hospital, Harlan, Kentucky
1949. Willson, J. Robert, University of Michigan Medical Center, Ann Arbor, Michigan (48104)
1948. Winston, Julius, 1616 Pacific Ave., Atlantic City, N. J. (08400)
1963. Wood, Horatio C., IV, Cincinnati General Hospital, Cincinnati, Ohio
1953. Zarafonetis, Chris J. D., Simpson Memorial Institute, University of Michigan, Ann Arbor, Michigan

Honorary Fellows

Limited to Fifty, of Whom Twenty May be Foreigners.

American

ELECTED

1964. Corner, George Washington, M.D., SC.D.(HON.), LL.D.(HON.), LITT.D.(HON.), 1810 Rittenhouse Square (3)
1959. Fay, Marion S., M.A., PH.D., SC.D.(HON.), LL.D.(HON.), Women's Medical College, Henry Ave. & Abbottsford Rd. (29)
1965. Gurin, Samuel, PH.D., SC.D.(HON.), University of Pennsylvania School of Medicine, 36th and Hamilton Walk (19104)
1936. Richards, Alfred Newton, PH.D., SC.D.(HON.), M.D.(HON.), LL.D.(HON.), Emeritus Professor of Pharmacology, School of Medicine, and Associate Trustee, University of Pennsylvania (4)
1958. Shryock, Richard H., PH.D., LL.D.(HON.), American Philosophical Society, Independence Square (6)
1947. Stone, Robert Spencer, M.D., University of California Medical School, San Francisco, Cal.

Foreign

1937. Dale, Sir Henry Hallet, C.B.E., F.R.S., O.M., M.D., F.R.C.P., 52 Queen Anne St., London, W. 1, England
1955. Mann, Ida, M.A., D.SC., M.B., B.S., L.R.C.P., D.O.M.S., F.R.C.S., Opthalmic Consultant to the Government of W. Australia, 56 Hobbs St., Nedlands, Perth, W. Australia.

Honorary Associate Fellows

1955. Clement, Martin W., 6 Penn Center Plaza (19103)
1955. Diemand, John A., President, Insurance Company of North America, 1600 Arch St. (2)
1964. Pew, J. Howard, Grays Lane & Mill Creek Rd., Ardmore, Pa.

Necrological List

Resident Fellows	*Date of Election*	*Date of Death*
1. Belk, William P.	May 12, 1930	March 8, 1965
2. Block, Louis H.	March 6, 1957	November 3, 1965
3. Chance, Burton	June 6, 1900	March 4, 1965
4. Donnelly, Joseph C.	January 9, 1933	September 28, 1965
5. Farrell, John T., Jr.	January 6, 1930	April 30, 1965
6. Gill, A. Bruce	October 6, 1920	November 7, 1965
7. Jeffers, William A.	March 5, 1941	September 29, 1965
8. Martucci, Albert A.	March 7, 1952	June 7, 1965
9. Massey, Franklin C.	February 4, 1953	July 9, 1965
10. Mullen, Edward A.	May 7, 1934	January 22, 1966
11. Norris, George W.	February 1, 1905	December 11, 1965
12. Orr, Theodore E.	January 6, 1936	April 20, 1965
13. Pfeiffer, Damon B.	October 6, 1915	January 6, 1966
14. Solis-Cohen, Leon	June 7, 1922	May 6, 1965
15. Ullom, Josephus T.	October 2, 1907	November 12, 1965
16. Vogel, Stoughton R.	May 7, 1941	January 3, 1966
17. Warner, Halsey F.	January 5, 1955	January 30, 1966
18. Williams, Joseph L.	February 3, 1965	July 1, 1965
19. Wolferth, Charles C.	June 5, 1918	December 26, 1965
Non-Resident	*Date of Election*	*Date of Death*
1. Shannon, Charles E. G.	March 4, 1908	February 2, 1965
Honorary-Foreign		
1. Schweitzer, Albert L. P.	May 16, 1962	September 4, 1965

(*Suggested Form of Bequest*)

I hereby give, devise, and bequeath to The College of Physicians of Philadelphia, a charitable and educational association organized under the laws of the Commonwealth of Pennsylvania and the executive offices whereof are located in the City of Philadelphia, the sum of . . . . . .

a. which sum shall be used for the general purposes of said association;

b. which sum shall be added to and become a part of the general endowment fund of said association;

c. which sum shall be used by said association preferably for the following purposes:

Index to Volume 33
1965–66

Agnew, D. H., 252
Albert, D. M., 264, 304
Alexander, J. D., 307*
Alpers, B. J., 307*
Alvarenga lecture, C. J. Lambertsen, 1, H. F. Harlow, 224
Andersonville, prison, 148
Antigens, drug, 171, diseases, 171
Appel, K. E., award, 303, 304
Art of Phila., Med., exhibition, 303
Arteriolarsclerosis, choroidal, 304
Artherosclerosis, hyperglyceridemia, 154
Atkinson, J. B., 305*
Autoimmunity, mechanisms, 19
Austrian, R., 306*

Barden, R. P., 306*
Baren, M., 148
Barness, L. A., 147, 149
Barnshaw, H. D., 304
Bauer, E. L., 216
Bedrossian, E. H., 148
Beerman, H., 305*
Behavior, surgery, 153, 194, primate, 224
Behrendt, T., 304
Belk, W. P., memoir of, 273
Bender, S. R., 147, 156
Bequest, suggested form, 335
Bethel, W. L., 296, 298*
Blain, D., psychiatrist, 304
Blood, hormones, 156, lipids, 155
Blumstein, G. I., 306 *bis**, 307*
Bongiovanni, A. M., 306*
Brest, A. N., 156
Brill, J. M., 147
Britain, mental health, 186
Brodsky, I., 148
Brooks, F. P., 308*
Brown, C. E., 305*
Bucher, R. M., 306*
Burnett, W. E., (present. Strittmatter), 303
Burns, treatment, 53

Camishion, R. C., 307*
Carbon monoxide, production, 150
Carroll, F. D., 148
Caswell, H. T., 148
Chamberlain, R. H., 306*
Chlorambucil, therapy, 151
Chouké lecture, M. Samter, 171
Clark, J. K., 306*
Coates, G. M., third mem. lecture, 304
Coburn, R. F., 150
Cohen, S. S., 238
Cohn, H. E., 307*
Collections, College, annual report, 300
College of Physicians of Phila.: Adm. staff, 308; Collections (ann. rep.), 300; Committees, 306; Fellows, 309; Lectures (1965), 303; Library (ann. rep.), 285; Mütter Museum (ann. rep.), 300; Officers, 305; President's address (Gibbon), 219; Secretary's rep., 279; Sections, (officers), 308, (programs and abstracts), 147; 304; Tour, 115; Treasurer's rep., 281
Community medicine, W. A. Steiger, 249
Cooper, D. A., 307*
Cooper, D. R., 307*
Cooper, M. D., 180
Cornelison, F. S., Jr., 153, 194

Darrah, James, 264
Davis, C. N., 306*
Davis, J. W., 306*
Deaver, J. M., 308*
Delinquency, parental roles, 304
Depression, reactive, 153
Dewees, A. L., memoir of, 269
Diabetes mellitus, eye, 304
Dietrich, H. J., Jr., 308*
Digestion, physiology, 121
Di Palma, J. R., 261
Donaldson, J. B., 306*
Downs, R. N., 264
Downs, T., McK., 264
Dripps, R. D., 306*
Duane, T. D., 304
Dunton, W. R., 264
Durant, T. M., Strittmatter Award, 303, 305*, 306*
Durrer, D., Newbold lecture, 159

Ear, endolymphatic sac, 304, surgery, 148, ultrasonography, 148
Eisman, S. H., 307*
Electrocardiography, unipolar, 159
Elias, E. J., 277
Elkinton, J. R., 306*, 307*
Elliott, F. A., 307*
Ellis, J. R., Anders lecture, 28
Elsom, K. A., 284, 305*
Enzymes, virus-induced synthesis of, 238
Epidemiology, career, 148

* Refers to the list of College officers, committees, sections, and administrative staff.

Evans, R. (Mrs.), 264
Eye, arteriolarsclerosis, 304, blepharospasm, 304, cryosurgery, choroid, 304, diabetic, 304, eyelids, 148

Fabbri, R., Jr., 202
Farrar, G. E., Jr., 306*, 307 *bis**
Farrell, J. T., Jr., memoir of, 275
Fay, M. S., 43
Fellows, list of, 309
Fewell, A. G., memoir of, 271
Finkelstein, A. K., 307*
Fontana, F., physiologist, 261
Frayer, W. C., 308*
French, G. N., 306*, 307*
Freudweiler, M., 147
Frobese, A. S., 307*
Fry, K. E., 307*

Gabrielsen, A. E., 180
Gachet, P-F., psychiatrist, 202
Geist, D. C., 305*
Genest, J., Newbold lecture, 303
Gershon-Cohen, J., 306*
Gibbon, J. H., Jr., pres. address, 219, 305*, 307*
Gibson, G. G., 308*
Gill, R. J., 307*, 308*
Glomerulonephritis, immunology, 19
Goldberg, H., 147
Goldberg, R. E., 148
Goldman, J. L., 148
Goldwein, M. I., 147, 150
Good, R. A., Newbold lecture, 180
Gout, pathogenesis, 147
Grotzinger, P. J., 305*

Hahn, G. A., 306*
Hahnemann Medical College, 147
Harbert, F., 148
Harkins, H. P., 308*
Harlow, H. F., Alvarenga lecture, 224
Hatfield lectures, C. A. Moyer, 53; S. S. Cohen, 238
Havens, W. P., Jr., 307*
Health, community, 249, education, 304, mental, 186, public, 304
Hemoglobin, degradation, 150
Heparin, fat tolerance, 155
Hinman, E. H., 305*
Hirsh, H., 151
His, W., Jr., 147
Hitchens lecture, M. E. Linden, 304
Hitschler, W. J., 308*
Hodes, P. J., 306*
Hodgkin's disease, chemotherapy, 151
Holloway, L. M., 294, 298
Holmes, W. L., 147, 157
Hormones, plasma, 156
Horwitz, O., 308*
House, W. F., 148
Hubbard, J. P., 308*
Huber, J. F., 305*
Hunter, J., creative surgeon, 197
Hyperglyceridemia, atherosclerosis, 154
Hyperlipidemia, treatment, 157
Hypersensitivity, immunologic, 19
Hypertension, renin-angiotensin, 303

Illness, way of life, 154
Immunobiology, developmental, 180, mechanisms, 19
Israel, S. L., 306*

Jackson, Chevalier, 49
Japan, medicine, 303
Jeffress, J. E., 154
Jones, R. E., 303, 305*, 308*
Joyner, C. R., Jr., 307*

Kahn, S. B., 148, 149
Kauffman, M. L., 308*
Kern, R. A., 303, 305*, 306*
Kidney, hypersensitivity, 19, immunology, 19
Kline, O. R., 308*
Klingensmith, P. O., 305*
Kolodziejski, T. J., 308*
Krewson, W. E., 3rd, 148
Kroman, H. S., 156
Krumbhaar, E. B., prize-essay, 104, 305*
Kuo, P. T., 147, 154

Lambertsen, C. J., Alvarenga lecture, 1
Lang, O. E., 308*
Langmuir, A. D., 148
Learner, N., 305*
Lectures, College, list of, 303
Lehman, J. S., 307*
Lewis, G. C., Jr., 148
Leymaster, G. R., 306*
Library: ann. rep., 285; historical notes, 293; committee, 305*
Linden, M. E., Hitchens lecture, 304
Lymphoid tissue, immunobiology, 180

Mann, B., memoir of, 52
Marden, P. A., 308*
Martucci, A. A., memoir of, 277
McCarty, D. J., 147
McClellang, G., 304
McClenahan, J. L., 305*
McCouch, E. A., 308*
McDaniel, W. B., 2d., 264, 267, 296, 308*
Macfarlane, C., 39
McCune, W. G., 307*
McGavic, J. S., 148
McGehee, E. H., 305*
McLean, J. M., de Schweinitz lecture, 304
MacNeill, N. M., memoir of, 216

Mancall, E. L. 307*
Mccray, P., Jr., 307*
Medical Documentation Service, 296
Medicine, Japanese, 303
Melanoma, metastatic, 148
Mellors, R. C., Mütter lecture, 19
Memoirs
Belk, W. P., 273
Dewees, A. L., 269
Farrell, J. T., Jr., 275
Fewell, A. G., 271
MacNeill, N. M., 216
Mann, B., 52
Martucci, A. A., 277
Mohler, R. G., 213
Schweitzer, A. L. P., 209
Shannon, C. E. G., 215
Mental health, Britain, 186
Methylmalonate, excretion, 149
Miller, M. M., 306*, 308*
Miller, T. G., 305*, 306*
Mitchell, J. McK., 306*
Mohler, R. W., memoir of, 213
Montgomery, H., 306, 307*
Montgomery, J. B., 213
Morse, D. P., 307*
Morse, E. H., 293, 308*
Moyer, C. A., Hatfield lecture, 53
Moyer, J. H., 306*
Mudd, E. H., 269
Mütter lecture, Mellors, 19
Musto, D. F., 121

Narrative, Ruschenberger, 264
Nealon, T. F., Jr., 305*
Necrology, 335
Nelson, A. D., 308*
Nemir, P., Jr., 306*
Neuritis, retrobulbar, 148
Newbold lectures, D. Durrer, 159, R. A. Good, 180
New York Acad. Med., 148, 304
Nicholson, J. T., 306*
Nodine, J. H., 147, 152
Norris, R. F., 305*, 306*

Ophthalmology, history, 264, 304
Osler, G. R., 264
Osler, W., 264
Oxygen, high pressure, 1

Padis, N., 305*
Patients, difficult, 151
Peltz, W. L., 307*
Pennsylvania Public Health Association, 148, 186, 304
Peterson, L. H., 305*
Peterson, R. D. A., 180
Philadelphia County Med. Soc., Joint Meetings, 303; Strittmatter Award (T. M. Durant), 303
Philadelphia Laryngological Soc., 304
Pillsbury, D. M., 306*
Poinsard, P. J., 147
Pool, J. L., 148
President's address (J. H. Gibbon), 219
Pressman, R. S., 307*
Preston, Ann, 43
Preventive medicine, medical education, 28
Prevost, J. L., medical historian, 139
Primates, socialization, 224

Quo, P. T., *see* Kuo, P. T.

Radbill, S. G., 215
Radbill, S. X, 252, 299, 305*
Rathmell, T. K., 306*, 307*
Rhoads, J. E., 305*, 306*
Rinzler, S. H., 148
Roberts, B., 305*, 307*
Robinson, V., medical historian, 144
Roentgenology, history, 304
Rogers, F. B., 139, 209, 267, 305*, 306*, 308*
Rollin, H. R., 186
Rose, E., 273
Rose, E. K., 306 *bis**
Rosen, S., 148 *bis*
Rossman, R. E., Krumbhaar prize-essay, 104
Rupp, C., 307*
Rush, A., 307*
Rush, B., medical thesis, 121
Ruschenberger, W. S. W., 264
Rynes, S. E., 307*

Samter, M., Chouké lecture, 171
Sargent, F., 304
Sarin, L. K., 148
Sataloff, J., 148
Schaeffer, J. P., 305*
Scheffey, L. C., 52, 305*
Scheie, H. G., 264, 308*
Schnabel, T. G., 305*, 307*
de Schweinitz lecture, J. M. McLean, 304
Schweitzer, A. L. P., memoir of, 209
Secretary's report, 279
Sections of the College: officers, 306*, programs and abstracts, 147, 304
Segal, B. L., 197
Serendipity, medical, 104
Shambaugh, G. E., Jr., Coates mem. lecture, 304
Shannon, C. E. G., memoir of, 215
Shannon, G. M., 148
Sharpless, F. C., 264
Shenkin, H. A., 304, 307*
Shimkin, M. B., 186, 306*, 308*
Shipman, J. S., 308*
Simmons, V. P., 306*
Slap, J. W., 152

Sloane, R. B., 148
Sodeman, W. A., 306*
Soll, D. B., 148
Spaeth, E. B., 148
Stainback, W. C., 307*
Stayman, J. W., Jr., 307*
Steiger, W. A., 151, 186, 249, 305*, 306*, 308*
Stokes, J., Jr., 306*
Strabismus, correction, 148
Streiten, J. W., 147
Strittmatter award, T. M. Durant, 303
Sturgis, K. R., 306*, 307*
Sturgis, S. B., 308*

Tellem, M., 148
Temple Univ., medical history, 139, community health, 249
Thompson, C. M., 306*
Thymus, immunobiology, 180
Tondreau, R. L., 306*, 308*
Treasurer's report, 281
Trommer, P. R., 307*
Tuddenham, W. J., 304
Tumen, H. J., 307*

Uhle, C. A. W., 305*
Ultrasonography, clinical, 148
Univ. of Pa., medical bicentennial, 121, 264, 304

Vander Veer, J. B., 306*
Van Gogh, V., artist, 202
Van Loon, E. L., 49
Vinblastin, therapy, 151
Vitamin B_{12}, deficiency, 149

Wade, E. N., 302, 308*
Waldo, A., 155
White, P., 150
Williams, W. J., 147, 149, 150
Wirz, H., 148
Wise, R. I., 307*
Woldow, A., 155
Wolferth, C. C., Jr., 147
Wolkowicz, M. I., 304
Woman's Medical College, 39, 43, 49
Wood, F. C., 305*
Wood, H. C., Jr., 308*

Zweiman, B., 307*

Vol. 33, No. 1
(4th Series)

July
1965

TRANSACTIONS & STUDIES

of the

College of Physicians

of Philadelphia

Contents

Medical Implications of High Oxygen Pressures (*Alvarenga Lecture XXIV*) ..... Christian J. Lambertsen 1

Immunologic Mechanisms in Glomerulonephritis: Hypersensitivity and Autoimmunity (*Thomas Dent Mütter Lecture LXXVII*) Robert C. Mellors 19

Preventive Medicine in Medical Education: An Internist's Viewpoint (*James M. Anders Lecture XXXXIV*) ..... John R. Ellis 28

The Woman's Medical College of Pennsylvania Catharine Macfarlane 39

Ann Preston: Dean of The Woman's Medical College of Pennsylvania, 1866–1872 ..... Marion S. Fay 43

Dr. Chevalier Jackson: President of The Woman's Medical College of Pennsylvania, 1935–1941 ..... Emily Lois Van Loon 49

Memoir of Bernard Mann (1883–1964) ..... Lewis C. Scheffey 52

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Preceding Number

Vol. 32, No. 4, April 1965

Contents

Presidential Address (*President's Annual Report*) John H. Gibbon, Jr. 149
Universities of Health and the Future of Medical Practice (*Mary Scott Newbold Lecture*) John E. Deitrick 153
Thomas Eakins (1844–1916): Painter, Sculptor, Teacher Gonzalo E. Aponte 160
Robley Dunglison: An Eminent Figure in Philadelphia Medicine Samuel X Radbill 164
The Development of Bronchoscopy at Jefferson John J. O'Keefe 171
Memoirs
Martin E. Rehfuss (1887–1964) W. Paul Havens, Jr. 175
Frederick H. Allen (1890–1964) Lauren H. Smith 177
Thomas Fitz-Hugh, Jr. (1894–1963) I. S. Ravdin 179
Philip H. W. Geisler (1925–1964) F. William Sunderman, Jr. 181
Annual Reports
Secretary, 183; Treasurer, 185; Library, 189; Mütter Museum and College Collections 200
List of College Lectures, 1964 202
Transactions of the Sections: Programs, and Abstracts from the Section on General Medicine 203
Officers, Committees, Sections and Administrative Staff of the College, 1965 216
List of Fellows 220
Suggested Form of Bequest 245
Index to Volume 32 246

Vol. 33, No. 4
(4th Series)

INDEX NUMBER

April
1966

TRANSACTIONS & STUDIES

of the

College of Physicians

of Philadelphia

Contents

President's Address (*President's Annual Report*). John H. Gibbon, Jr. 219
The Primate Socialization Motives (*Alvarenga Lecture XXV*)
Harry F. Harlow 224
Virus-Induced Synthesis of Enzymes (*Nathan Lewis Hatfield Lecture L*)
Seymour S. Cohen 238
The University in the Forefront of Community Action
William A. Steiger 249
David Hayes Agnew, M.D. (1818–1892). Samuel X Radbill 252
Felice Fontana (1720–1805): The Forgotten Physiologist
Joseph R. Di Palma 261
Library Historical Notes. W. B. McDaniel, 2d 264
A Decade of Harvest: *Ave atque vale* to the Editor, Fred B. Rogers, M.D.
W. B. McDaniel, 2d 267
Memoirs
Lovett Dewees (1880–1965). Emily Hartshorne Mudd 269
Alexander Garrison Fewell (1884–1965). Warren S. Reese 271
William Parks Belk (1889–1965). Edward Rose 273
John Thompson Farrell, Jr. (1897–1965). Mario A. Cinquino 275
Albert Americo Martucci (1900–1965). Elmer J. Elias 277
Annual Reports
Secretary, 279; Treasurer, 281; Library, 285; Mütter Museum and College Collections, 300.
List of College Lectures, 1965. 303
Transactions of the Sections. 304
Officers, Committees, Sections and Administrative Staff of the College, 1966. 305
List of Fellows. 309
Suggested Form of Bequest. 335
Index to Volume 33. 336

PUBLISHED AT BALTIMORE, MARYLAND

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Preceding Number

Vol. 33, No. 3, January, 1966

Contents

The Human Heart: Some Aspects of its Excitation (*Mary Scott Newbold Lecture LXXXIX*) ..... Dirk Durrer 159

Drug Antigens and the Diseases Which They Produce (*Hira S. Chouké Lecture VI*) ..... Max Samter 171

The Central Lymphoid Tissue in Developmental Immunobiology (*Mary Scott Newbold Lecture LXXXVII*) .. Robert A. Good et al. 180

Community Mental Health Care in Britain? ..... Henry R. Rollin 186

Behavioral Reactions to Surgical Procedures. . . Floyd S. Cornelison 194

John Hunter (1728–1793): Creative Surgeon ..... Bernard L. Segal 197

Dr. Paul-Ferdinand Gachet: Vincent Van Gogh's Last Physician Remo Fabbri, Jr. 202

Memoirs:

Albert Schweitzer (1875–1965) ..... Fred B. Rogers 209

Roy W. Mohler (1892–1964) ..... John B. Montgomery 213

Charles E. G. Shannon (1875–1965) ..... Sidney G. Radbill 215

Norman M. MacNeill (1886–1965) ..... Edward L. Bauer 216

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